ASSESSMENT OF FIVE-YEAR MYOPIA INTERVENTION STUDY IN TAIPEI (MIT) PROGRAM FOR DELAYING MYOPIA PROGRESSION IN TAIPEI PRIMARY SCHOOLS

by
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A dissertation submitted to Johns Hopkins University in conformity with the requirements for the degree of Doctor of Public Health

Baltimore, Maryland
April 2020

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Abstract

Myopia is getting global public concern owing to the rise in its prevalence worldwide and associated ocular disease burden. Myopia starting at early age is prone to become high myopia and finally bring a heavy public health and socio-economic burden. The report from World Health Organization (WHO) 2020 estimates that by year 2050, there is going to be 4.95 billion or 52.0% of the world population getting myopia and almost 0.925 billion people or 10.0% of the world population having high myopia. The myopia prevalence for primary school students in Taiwan at a progression rate around 1.0 - 1.2D per year poses the second highest position worldwide. Both genetic and environmental risk factors contribute to myopia. The intensive studying, education pressure and convenient access of 3C products make the eyes overloaded. Atropine of 0.125%, 0.25% and 0.5% medium concentration modified by season integrated with interventions “853240” of MIT (Myopia Intervention Study in Taipei) program are used to improve the effect on myopia control.

Three topics are designed to investigate (1) the effect of seasonal atropine combined MIT program using repeated measures mixed-effects model and

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Generalized Estimating Equations (GEE) model, (2) the cost-effectiveness using heabs, bootstrapping and heapbs module, and (3) the vision-related quality of life using Taiwan Visual Function Questionnaire (Twn VFQ-25) for primary schoolchildren. The result of medium-concentration (0.125%, 0.25% or 0.5%) atropine modified by season integrating with MIT healthy lifestyle interventions “853240” reveals less myopia progression (0.33 D/y) in MIT group compared to (0.64 D/y) in non-MIT controls. The result of low ICER and high INB after following-ups for ≥ 4 years suggests cost-effective as long as willing-to-pay (w2p) equal to or higher than NTD 1,000. Twn VFQ-25 is valid for evaluating the vision-related quality of life and reveals no deteriorated effect after atropine use for primary schoolchildren.

In conclusion, the longer the eye, the worse the myopia; where axial length elongation remains a biomarker for myopia progression. Modified medium-concentration of atropine combined with MIT program will not cause major side effects in quality of life and may play a cost-effective role in preventing myopia progression.

Primary Reader and Advisor: Leiyu Shi

Secondary Reader: Yiing-Mei Liou.

Acknowledgments

Professor Leiyu Shi instructs the guidelines for dissertation writing, Professor Yiing-Mei Liou offers the MIT dataset related to Harvard Vision Center and instructs the basics for questionnaire design and analysis, and Dr. Xiangrong Kong as my statistical tutor instructs me the proper statistical methods and skills, Professor Miaw-Chwen Lee provides useful comments on cost-effectiveness analysis. I am very appreciated all mentors mentioned above, Dr. Jessica Yeh as being the chair and Dr. Lilly Engineer as an alternate for serving in both of my oral committees. I would also like to express my gratitude to Dr. Junya Zhu for serving in my thesis proposal and preliminary oral examination committee, and to Dr. Hong Kan as well or serving in my dissertation readers and final oral examination committee.

Dedication

This dissertation is dedicated to my parents, Li-Sen Lu and Cai-E Ou, for their patient waiting and love; to my sister Ching-Fen Lu and my brother Sheng-Ta Lu for their bearing of taking care of parents; to my wife Lillian, my three sons Byron, Jason and Chris and my daughter-in-law Lilly for their encouragements and supports.

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Chapter 1

Introduction

Importance of myopia

Myopia is a common worldwide and most cases can improve their visions by glasses, contact lens, orthokeratology lens, and refractive surgery; thus it is overlooked and treated as benign disorder. However, some serious complications especially from those with higher or pathologic myopia (greater than 6 diopter (D)) are even blinding threats such as dense cataracts, glaucoma, macular degeneration and retinal detachment (Bourke, Loughman, Fltcroft, Loskutova, & O'Brien, 2019; Morgan & Rose, 2019; Saw, Gazzard, Shih-Yen, & Chua, 2005). Not only the ocular complications, the socio-economic burden is becoming a national and global public concern. (Leo & Young, 2011; Ramamurthy et al., 2015; Reeves et al., 2012)

Prevalence of Myopia

The significant increase of global prevalence of myopia and high myopia makes it an important issue of public health. Kuang estimated in a report for World Health Organization (WHO) that 153 million people worldwide had visual impairment due to uncorrected refractive error (Kuang et al., 2016). Holden revealed that 22.9% of the world population or 1.4 billion individuals are myopic, and high myopic people in year 2000 are 63 million persons or 2.7% of the world population (Holden, B. A. et al., 2016). Growing prevalence and comorbidities associated with myopia make it a threatening vision disorder. Incidence of myopia is rising and the prevalence of myopia in the US has increased from 25% to 44% in the last 30 years (Miraldi Utz, 2016). The prevalence of myopia in Asian countries can be as high as 80% among young adult populations (Miraldi Utz, 2016). By year 2020, the prevalence of myopia is expected to be about 2.5 billion persons (Miraldi Utz, 2016). Holden predicted that by year 2050, there is going to be 4.95 billion, almost doubled Utz's estimates for year 2020, or 52.0% (Figure 1-1) of the world population getting myopia and almost 0.925 billion people or 10.0% (Figure 1-2) of the world population having high myopia (Holden, B. A. et al., 2016).

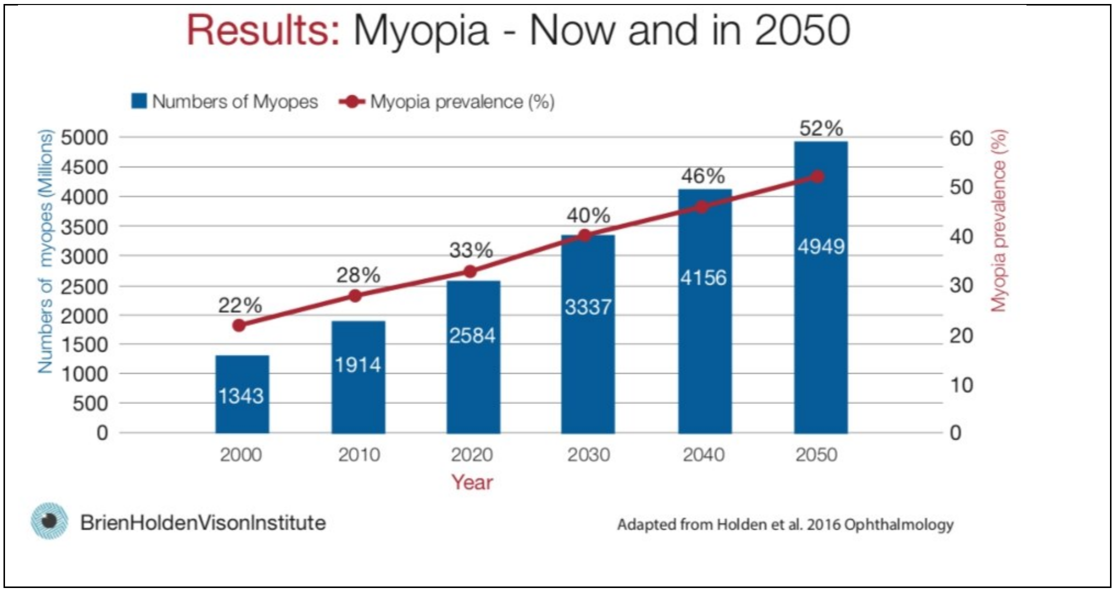


Figure 1-1 Numbers of cases (blue) and prevalence (red) of myopia worldwide between 2000-2050.

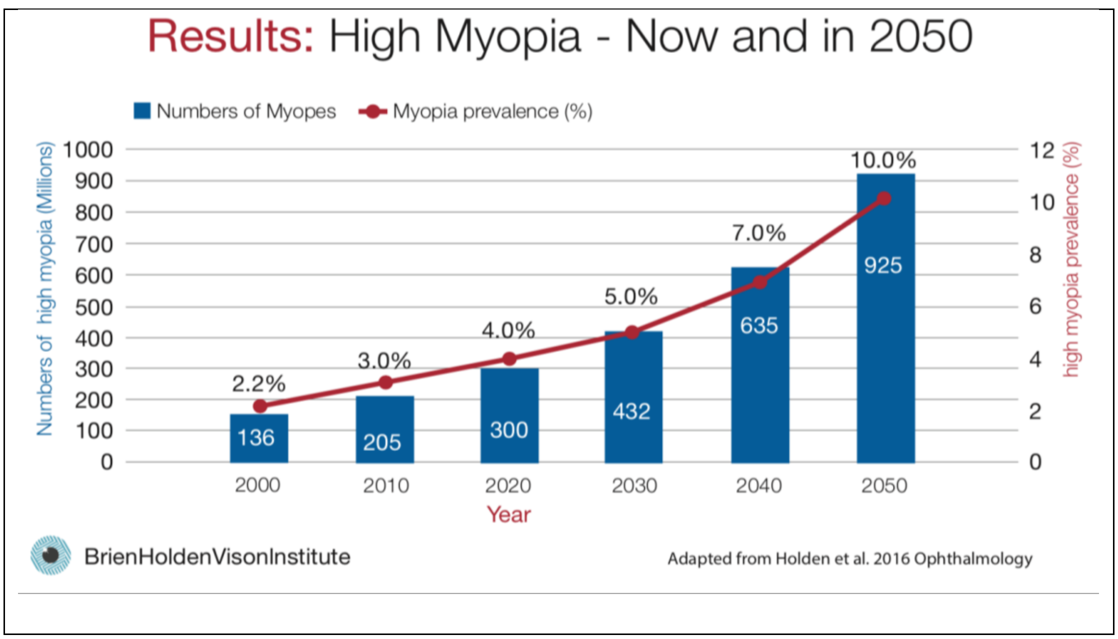


Figure 1-2 Numbers of people (blue) and prevalence (red) of high myopia worldwide between 2000-2050.

Myopia in Taiwan

In 2010 the prevalence rate of myopia in Asia-Pacific high-income area and East Asia area is 48.8% and 47.0% respectively (B. A. Holden et al., 2016). As a “Kingdom of myopia” (Liou, 2019), the prevalence of myopia in Taiwan is higher than those two areas. In Taiwan, for primary schoolchildren at first grade of age 7: it was 19.6% in 2006, 21.5% in 2010 and 26.5% in 2018; at sixth grade of age 12: it was 61.8% in 2006, 65.8% in 2010 and 63.3% in 2018 respectively. So, the myopia prevalence of the sixth grade (63.3%) was 2.39 folds higher than the first grade (26.5%) in year 2018. The situation gets worse among high school students, at twelfth grade of age 18: the prevalence of myopia was 85.10% in 2006, 87.2% in 2010 and 83.5% in 2018 respectively as shown in Table 1-A (HPA, 2018). The myopia prevalence in primary school students in Taiwan was the second highest, just lower than that in Singapore. (Liou, 2019)

Table 1-A Myopia* prevalence of age 6 to age18 students in Taiwan from year 1986 to 2018

Year / Grade	1986 (%)	1990 (%)	1995 (%)	2000 (%)	2006 (%)	2010 (%)	2018 (%)
1st Grade	3.0	6.5	12.8	20.4	19.6	21.5	26.5
2nd Grade	-	-	-	-	33.5	36.8	32.6
3rd Grade	-	-	-	-	40.0	45.4	41.1
4th Grade	-	-	-	-	46.0	53.1	49.2
5th Grade	-	-	-	-	51.8	58.9	56.7
6th Grade	27.5	35.2	55.8	60.6	61.8	65.8	63.3
9th Grade	61.6	74.0	76.4	80.7	77.1	76.9	77.4
12th Grade	76.3	75.2	84.1	84.2	85.1	87.2	83.5

* From 1986 to 2018, myopia defines myopia ≥0.25D

The prevalence of high myopia increases from 0.7% at year 1986 to 10.3% at year 2018, i.e. 14.7 folds higher, for sixth grade primary schoolchildren as shown in Table 1-B (HPA, 2018).

Table 1-B High Myopia* prevalence of age 6 to 18 students in Taiwan from year 1986 to 2018

Grade \ Year	1986 (%)	1990 (%)	1995 (%)	2000 (%)	2006 (%)	2010 (%)	2018 (%)
1st Grade	0.1	0.2	0	0.2	0	0	1.2
6th Grade	0.7	0.5	2	2.4	2.5	3.4	10.3
9th Grade	3.1	6.1	7.5	12.7	6.6	-	28.0
12th Grade	9.2	6.7	15.9	20.8	16.9	-	35.7

* High myopia defines myopia ≥ 6.00D

Risk factors of myopia

Genetic and environmental risk factors both contribute to myopia. Those who developed myopia at much younger age are easily to become pathologic high myopia in later life (Ramamurthy, Lin Chua, & Saw, 2015; Wu, Tsai, Wu, Yang, & Kuo, 2013). Familial aggregation is noted in those who have high myopia with pathogenesis significantly associated with genetic factors. Linkage analysis, candidate gene authentication, genome-wide association study (GWAS), and next-generation sequencing (NGS) have applied in genetic studies and identified many myopia-associated loci and genetic variants or mutations (Cai, Shen, Chen, Zhang, & Jin, 2019). The rapid increase in myopia prevalence is implicit of environmental influences in addition to any genetic influences on eye growth (Harb & Wildsoet, 2019).

Breastfeeding (Liu, Ye, Wang, Cao, & Zhang, 2018) and early life factors (Williams et al., 2019) were reported to affect myopia progression later in life. Higher levels of education and near work are associated with development of myopia (Bez et al., 2019; Guan et al., 2019; Lee et al., 2017; Miraldi Utz, 2016). To obtain higher education and get a better job are the goals of most Taiwanese.

Thus intensive studying, education pressure and convenient access of 3C products such as smart phone, smart watch, iPad, computer and TV make the eyes overloaded.

Interventions

Effective interventions and managements are critical for schoolchildren to prevent early-onset myopia (Chua et al., 2016)and prevent pathological high myopia afterwards. (Leo & Young, 2011; Myrowitz, 2012; Ramamurthy et al., 2015)

We have demonstrated that atropine administration with seasonal modification is effective to delay myopia progression (Lu & Chen, 2010). By further introducing and efficient interventions and management, so called MIT (Myopia Investigation in Taipei City) program, we desire to improve the effect on delaying myopia progression. MIT program emphasizes on healthy life interventions on six perspectives in children daily life, just as the slogan “853240” revealed: get enough 8-hr sleep (8), eat 5 colorful vegetable and fruits (5), keep 3 triangular seating position (3), outdoor activities for at least 2 hours every day (2), away from 4 3C products including iPhone, iPad, computer and TV (4), and 10–minute rest every 30-minute eye using (0).

Incentives

The primary school students in Taipei City were recruited in MIT program and offered 1-2 free ocular exams per year at contracted ophthalmic clinics or hospitals. To improve the implementation of these interventions, we recommended the schoolchildren to wear transition glasses that would turn darker under strong sunlight with UV exposure. Progressive glasses were prescribed if they met trouble at reading or writing. Teachers were asked to encourage students leaving classroom at recess section, parents were recommended to assist schoolchildren to have enough sleep, prepare nutrients-rich meals and away from garbage foods for their kids and arrange outdoor activities during weekends or holidays as well. Teachers and parents should be aware the sitting position of schoolchildren and restrict using of 3C products. There were Facebook and websites to communicate with parents and teachers as well. Awards for students keeping bare vision of 20/20 were announced at graduation ceremony with a coupon gift to encourage them to keep good study- and life-style at school and home for future myopia prevention.

There are three questions remained to be clarified. The first question: what is the effect of modified atropine combined with MIT program for myopia control in primary schoolchildren? The second question: is the treatment program cost-effective or not? The third question: will atropine treatment after a period of time affect the children’s quality of life and their learning? To answer those questions mentioned above we conduct the following research.

Study topics

This study is composed of three topics for research on this global important issue of public health:

Topic 1. Association of Seasonal Atropine Eyedrops and MIT Program for Five-year Myopia Control of Primary School Students in Taipei.

Comparing the spherical equivalents and axial lengths between MIT and non-MIT group to illustrate the positive association of atropine eyedrops and the interventions of MIT program for preventing myopia progression.

Topic 2. Cost-effectiveness Analysis for the Five-year MIT Program of Myopia Control in Taipei Primary School Students.

Applying heabs, bootstrapping and heapbs module to analyze ICERs and INBs between MIT and non-MIT group for five-year follow-ups.

Topic 3. Assessment of the Taiwan Visual Function Questionnaire (Twn VFQ-25) for Primary School Students.

Assessing the validity of Twn VFQ-25 (Hinterlong, Holton, Chiang, Tsai, & Liou, 2019; RAND, 2019)and using that questionnaire to analyze the impacts of atropine eye drops on schoolchildren's near and distance vision between MIT and non-MIT group.

Significance

This study is going to provide useful references and guidelines for policy maker and clinical professionals in reducing learning burden and myopia progression among schoolchildren and reaching cost-effectiveness for the entire society in long run.

Related aims

Aim 1. Extending MIT program to kindergartens and junior high schools, even to high schools.

Aim 2. Encouraging other cities or counties, urban or rural schools to adopt the successful experiences from MIT program.

Study and statistical methods adopted

Professor Leiyu Shi instructs the guidelines for dissertation writing, and Professor Yiing-Mei Liou offers the MIT dataset related to Harvard Vision Center and instructs the basics for questionnaire design and analysis. In addition to intensive literature review, I have studied the analytical methods from Johns Hopkins teaching material from classes and Stata manual, through UCLA teaching website (UCLA, 01072020; UCLA, 08042019)and discuss the proper statistical methods with my statistical tutor, Dr. Xiangrong Kong and Dr. Daniel Gallacher in UK. Stata/IC 15.1 (StataCorp LP, TX, USA) and Microsoft Excel (14.5.2) were applied for statistical analyses. Each topic contains several statistical analysis tools, modules and methods adopted as follows:

Topic 1. Association of Seasonal Atropine Eyedrops and MIT Program for Five-year Myopia Control of Primary School Students in Taipei.

Student t-test, repeated measures mixed-effects model analysis (UCLA, 08042019), and Generalized Estimating Equations (GEE) model were applied.

Topic 2. Cost-effectiveness Analysis for the five-year MIT Program of Myopia Control in Taipei Primary School Students.

Student t-test, heabs, bootstrapping and heapbs module (Gallacher, 02182020; Gallacher & Achana, 2018) were applied.

Topic 3. Assessment of the Taiwan Visual Function Questionnaire (Twn VFQ-25) for Primary School Students.

Student t-test, ordered logistic regression model were applied.

Chapter 2

Association of Seasonal Atropine Eyedrops and MIT Program for Five-year Myopia Progression of Primary School Students in Taipei

Abstract

Purpose

To investigate whether seasonal atropine eye drops and MIT (Myopia Intervention Study in Taipei) program have synergic effect in delaying myopia progression among a cohort of primary school students in Taipei city for five-year follow-up.

Design

A prospective study with seasonal modification of atropine eye drops and daily life intervention using secondary dataset from students in Cohort I of MIT program and controls from students in non-MIT program.

Table 2-T Terminology

Terminology	Meaning/Math Equation	Unit
Spherical equivalent (se)	= sphere + ½ astigmatism	Diopter (D)
Myopia progression (dse)	= se (time 0) – se (time t)	Diopter (D)
Axial length (al)	= length of eye globe	Mini meter (mm)
Axial elongation (dal)	= al (time t) – al (time 0)	Mini meter (mm)

Participants

The second-grade students from all public primary schools in Taipei willing to join MIT program (TCHIRB-1020501) were recruited in September 2013 as Cohort I study subjects of MIT.   The participation rate with completed cycloplegic autorefraction measures taken on both eyes was 59.8% (11,590 out of 19374).

Those who joined MIT program had the privilege to get free ocular examination and vision test, sponsored by Taipei City Health Bureau, at all contracted hospital ophthalmology departments or private ophthalmic clinics and obtained a “Vision Protection Passport” with the intervention tips inside. Students from non-MIT group served as controls. MIT students were followed up every one to two months for continuing atropine therapy, however non-MIT students visited ophthalmic clinic every semester only for finishing the “Vision Exam Sheet” required by Ministry of Education. All were followed up to five years until they graduated from primary school at sixth grade in June 2018. Enrollment criteria included the both eyes having at least spherical equivalent of at least -0.25 diopters (D), astigmatism power no more than 2.0 D and corrected vision as 1.0 (20/20). Students with previous ocular trauma, amblyopia, traumatic cataract, keratoconus, myopia over -10.0D, ocular hypertension, glaucoma or OK (orthokeratology) lens user were excluded.

Methods

Atropine eye drops with three different concentrations of 0.1%, 0.25%, or 0.5% were used with modification according to seasonal sunlight intensity and the severity of myopia. Anti-UV sunglasses were prescribed for subjects while they had outdoor activities and progressive spectacles were given for children who had difficulty in reading or writing.

We used “853240” as multifactorial interventions in MIT program to enhance and improve the effects of atropine. “8” stood for 8-hr sound sleep; “5” for 5 colorful vegetables and fruits; “3” for 3 ninety angles (ankle, knee and hip); “2” for 2-hr outdoor activities daily; “4” for less using 4 3Cs (TV, iPad, computer, cell phone); “0” for 10–minute rest every 30-minute eye using. Refractive error, uncorrected and corrected visual acuity, intraocular pressure (IOP), and axial length were measured under cycloplegic condition per six months with follow-ups for 5 years. All secondary data were retrieved from schoolchildren of MIT and non-MIT group at Harvard Vision Center. Rates of changes of spherical equivalents and axial lengths using longitudinal ocular measurements were compared between MIT group (n = 364) and non-MIT group (n =174) using repeated measures mixed-effects model analysis (UCLA, 08042019) and cross sectional relationship between myopia and axial length were analyzed by Generalized Estimating Equations (GEE) model. Stata/IC 15.1 was applied for statistical analysis.

Main Outcome Measures

Spherical equivalents and axial lengths.

Results

Refractive data were available for 538 participants consisting of 364 students from MIT group (n = 364) and 174 students from non-MIT group (n = 174). The basic demographic characteristics, including age, gender, and parents' myopia status, showed no statistic significances at recruitment (time 0). Myopia progression (increment of mean spherical equivalents) during the five-year study period was 3.24±1.08 D and 1.69 ±1.06 D in the non-MIT and MIT groups, respectively. Axial length elongations between baseline and five years later were 1.01±0.44 mm and 0.67±0.30 mm in the non-MIT and MIT groups respectively. The cross sectional relationship between myopia progression and axial elongation were 1.44 ±0.04D /mm and 1.06 ±0.05D /mm in the non-MIT and MIT groups respectively.

Conclusions

Seasonally modified atropine eye drops combined with MIT program; compared to non-MIT group, reveal positive effect on delaying myopia progression in primary school children in Taipei.

Introduction

Myopia is a common ocular disorder and treated as benign condition; in most cases their visions can be improved by glasses, contact lens, orthokeratology lens, and refractive surgery. However, some complications especially from those with higher or pathologic myopia (greater than 6 diopter (D)) are even blinding threats such as dense cataracts, glaucoma, macular degeneration and retinal detachment (Morgan, Ohno-Matsui, & Saw, 2012; Saw, Gazzard, Shih-Yen, & Chua, 2005).

The significant increase of global prevalence of myopia and high myopia makes it an important public health issue. In year 2000, there were approximately 1406 million people (22.9% of the world population) with myopia 0.50D or more and 163 million people (2.7% of the world population) with myopia 5D or more (B. Holden et al., 2014). By year 2050, the predicted global prevalence of myopia 0.5D or more is as high as 52.0% (Figure 1-1), Chapter 1) and 10.0% of the world population (Figure 1-2), Chapter 1) with myopia 6D or more. Asia-Pacific, high-income area and East Asia are the two areas of highest prevalence rate from 2000 through 2050 (B. A. Holden et al., 2016). In 2010 the prevalence rate of myopia in Asia-Pacific, high-income area and East Asia area is 48.8% and 47.0% respectively (B. A. Holden et al., 2016).

The prevalence of myopia is higher than those two areas here in Taiwan. For primary school children at first grade of age 7: it was 19.6% in 2006, 21.5% in 2010 and 26.5% in 2018; at sixth grade of age 12: it was 61.8% in 2006, 65.8% in 2010 and 63.3% in 2018 respectively. The situation gets worse among high school students, at twelfth grade of age 18: the prevalence of myopia was 85.10% in 2006, 87.2% in 2010 and 83.5% in 2018 respectively (HPA, 2018). Genetic and environmental risk factors both contribute to myopia. Those who developed myopia at much younger age are easily to become pathologic high myopia in later life (Ramamurthy, Lin Chua, & Saw, 2015; Wu, Tsai, Wu, Yang, & Kuo, 2013) . The social and economic burden could not be overemphasized in addition to the ocular complication. (Chen, Lee, Pigg, Huang, & Yen, 1990; Leo & Young, 2011; Meng, Butterworth, Malecaze, & Calvas, 2011; Ramamurthy et al., 2015; Reeves et al., 2012; Zheng et al., 2013)

Some studies have shown that a child with two myopic parents is 5-7 times more likely to have myopia compared to a child with one or neither parents with myopia (Miraldi Utz, 2016). These studies, however, cannot control for gene-environment interactions. For example, children of myopia parents tend to spend more time in environments that increase the risk of myopia (Miraldi Utz, 2016). Evidence of gene-environment interactions has shown that having a risk allele changes retinal image and contrast processing and can lead to myopia in those who read intensely (Enthoven et al., 2019; Miraldi Utz, 2016; Pozarickij, Williams, Hysi, Guggenheim, & UK Biobank Eye and Vision Consortium, 2019) . Breastfeeding (Liu, Ye, Wang, Cao, & Zhang, 2018) and early life factors (Williams et al., 2019) were reported to affect myopia progression later in life.

Higher levels of education and near work are associated with development of myopia (Bez et al., 2019; Guan et al., 2019; Lee et al., 2017; Miraldi Utz, 2016). To obtain higher education and get a better job are the goals of most Taiwanese.

Thus intensive studying, education pressure and convenient access of 3C products such as smart phone, smart watch, iPad, computer and TV make the eyes overloaded.

Many studies have shown that exposure to natural light through outdoor play is preventative against progression of myopia (Cao, Wan, Yusufu, & Wang, 2019; Guggenheim et al., 2012; Miraldi Utz, 2016). Lower rates of myopia occur where environmental and behavioral risk factors are not present, such as rural areas where exposure to natural light is more common than in urban areas (Cao et al., 2019; Miraldi Utz, 2016).

The axial length elongation (dal) is highly associated with myopia progression (Lu, P. C. & Chen, 2010; Miraldi Utz, 2017) where myopia was measured after fully cycloplegic dilatation of pupil and progression defined the increment of myopia magnitude. However fully cycloplegic dilatation sometimes is hard to define in real clinic or examination situation and is subjectively judged. In this study the axial length (al) will be measured using IOL master (Carl Zeiss Meditec AG), a non-contact optical instrument, and the data will be retrieved more objectively. (Kumaran, Htoon, Tan, & Chia, 2015; Lu & Chen, 2010; Meng et al., 2011; Swarbrick, Alharbi, Watt, Lum, & Kang, 2015)

Interventions targeting myopia include optical correction, refractive surgery, pharmaceutical interventions, vision therapy, or orthokeratology (ortho-K) and are influenced by patient age, motivation to wear and comply with care procedures of contact lenses, corneal physiology, and financial circumstances. (Goss et al., 2006) Eyeglasses can be more affordable and are generally safer, however, they are not effective for prevention of myopia progression. Soft contact lenses can pose a risk of corneal infection (Charm & Cho, 2013; Cho & Cheung, 2012). Ortho-K is a brand of rigid contact lenses that are worn at night, and some effects have been shown in controlling myopia, however, it also poses a risk of corneal infection in addition to its high cost (Charm & Cho, 2013; Cho & Cheung, 2012; Sun et al., 2015; Zhou, Xie, Wang, Guo, & Yang, 2015) . Effective interventions and managements are critical for school-aged children to prevent early-onset myopia and prevent pathological high myopia afterwards. (Leo & Young, 2011; Myrowitz, 2012; Ramamurthy et al., 2015)

In 1999, Taiwan was coined the “the island of myopia” and “myopia capital of the world.” The Ministry of Health and Welfare reported that 90% of university students in Taiwan were myopic, along with 85% of high school students, 75% of junior high school students, and 12% of first-grade students (Chang, 1999). Myopia and high myopia prevalence of school-aged students from year 1986 to 2018 are illustrated in Table A and Table B (Chapter 1) respectively, where we can see the myopia prevalence in first grade student was 26.5% in year 1986 and increased to 63.3% in year 2018, as 2.39 folds higher. (HPA, 2018) The myopia prevalence in primary school students in Taiwan was the second highest, just lower than that in Singapore. (Liou, 2019)

Myopia progression is influenced by multiple factors, such as breastfeeding (Liu et al., 2018), some sociological and lifestyle trends in early life including rates of maternal education, fertility treatment, early schooling and computer games (Williams et al., 2019). We have demonstrated that atropine administration with seasonal modification is effective to delay myopia progression (Lu & Chen, 2010). By further introducing and efficient interventions and management, so called MIT (Myopia Investigation in Taipei) program, we desire to improve the effect on delaying myopia progression. MIT program emphasizes on healthy life interventions on six perspectives in children daily life, just as the slogan “853240” revealed: get enough 8-hr sleep (8), eat 5 colorful vegetable and fruits (5), keep 3 triangular seating position (3), outdoor activities for at least 2 hours every day (2), away from 4 3C products including iPhone, iPad, computer and TV (4), and 10–minute rest every 30-minute eye using (0). The primary school students in Taipei City were recruited in MIT program and offered 1-2 free ocular exams per year at contracted ophthalmic clinics or hospitals. To improve the implementation of these interventions, we recommended the schoolchildren to wear transition glasses that would turn darker under strong sunlight with UV exposure. Progressive glasses were prescribed if they met trouble at reading or writing. Teachers were asked to encourage students leaving classroom at recess section, parents were recommended to assist schoolchildren to have enough sleep, prepare nutrients-rich meals and away from garbage foods for their kids and arrange outdoor activities during weekends or holidays as well. Teachers and parents should be aware the sitting position of schoolchildren and restrict using of 3C products. There were Facebook and websites to communicate with parents and teachers as well. Awards for students keeping bare vision of 20/20 were announced at graduation ceremony to encourage them to keep good study and life style at school and home.

The study is going to provide useful references and guidelines for policy maker and clinical professionals in reducing learning burden and myopia progression among schoolchildren and reaching cost effectiveness for the entire society.

Methods

Those second-grade schoolchildren from Taipei public primary schools having joined MIT program (TCHIRB-1020501) and followed-up at Harvard Vision Center were eligible for this study. Among all 19,374 grade 2 schoolchildren in Taipei City, there were 16,486 (85.1%) students' parental consent forms and parent-administered questionnaires collected. During the period between July 2013 and September 2013, only 12,019 (62.0%) schoolchildren got eye examinations and eventually a total of 11,590 (59.8%) cases had completed cycloplegic autorefraction measurements on both eyes. (Tsai et al., 2015)

All cases with both eyes having spherical equivalent at least -0.25 D, astigmatism less than 2.25 D and corrected visual acuity up to 1.0 (20/20) were recruited and followed from September 2013 to June 2018 for five years. Exclusion criteria for eyes included having previous ocular trauma, amblyopia, cataract, keratoconus, myopia over -10 D, ocular hypertension, glaucoma or wearing OK lenses.
Eye drops with 0.1% atropine were installed in summers, 0.25% atropine used in springs and falls, and 0.5% atropine for winter use. The frequency of instillation was even reduced to once or twice a week for those having low myopia (-0.75D to -0.25 D). Transition or anti-UV glasses were prescribed for outdoor purposes

and progressive glasses were prescribed for those needed.

The so called “853240” healthy living interventions were applied in day-to-day activities to enhance and improve the effects of atropine. “8” stood for sound sleep for 8 hours; “5” for eating 5 colorful vegetables and fruits every day; “3” for sitting position with 3 ninety angles (ankle, knee and hip), 2 flat planes (both arms resting flat on desk) and 1 line for ear, shoulder and hip; “2” for outdoor activity at least 120 minutes daily; “4” for reducing use of 4 3Cs (TV, iPad, computer, cell phone) for one hour at most per day; “0” for 10–minute eye rest every 30-minute use.

The biometrical data of refractive error, uncorrected and corrected visual acuity, intraocular pressure (IOP), and axial length were documented under cycloplegic condition every six-month follow-up. Parents’ myopia status was documented in addition to schoolchildren age and gender. All secondary data were retrieved from Harvard Vision Center and Cohort I Study of MIT Program. Students meeting the inclusion criteria from non-MIT group served as controls.

By using the longitudinal ocular measurements, repeated measures mixed-effects model analysis (UCLA, 08042019) was applied to compare the rates of changes of myopia equivalents and axial lengths between MIT group (n = 364) and non-MIT group (n = 174) and Generalized Estimating Equations (GEE) model was applied to analyze the cross sectional relationship between myopia equivalents and axial lengths. Endpoints from both eyes will be pooled in combined analysis using generalized estimating equations to allow for the correlation between eyes within participant. Stata/IC 15.1 (StataCorp LP, TX, USA) software was used for statistical analyses.

Results

At recruitment (time zero), mean age was 8.25±0.28 and 8.27±0.31 years in MIT and non-MIT group (P=0.41), respectively. Mean spherical equivalent was -0.81 ±0.43 D and -0.87±0.58 D in MIT and non-MIT group (P=0.14), respectively. Mean axial length was 23.48±0.54 mm and 23.45±0.70 mm in MIT and non-MIT group (P=0.60), respectively. There were 48.90% and 55.17% boys in MIT and non-MIT group (P=0.20), respectively. High myopia (>= 6.0 D) rate of parents was 47.80% and 55.17% in MIT and non-MIT group (P=0.22), respectively. The basic demographic characteristics showing no statistic significances were summarized in Table 2-1.

Table 2-1 Demographic characteristics

At recruitment (time 0)	MIT	Non-MIT	p value
Spherical equivalent* (D)	-0.81±0.43 (-0.38 to -3.00)	-0.87±0.58 (-0.25 to -4.25)	P=0.14
Axial length* (mm)	23.48±0.54 (22.39 to 25.18)	23.45±0.70 (22.15 to 25.35)	P=0.60
Age* (years)	8.25±0.28 (7.69 to 8.75)	8.27±0.31 (7.75 to 8.75)	P=0.41
Gender (male %)	48.90%	55.17%	P=0.20
High myopia of parents (D)	47.80%	55.17%	P=0.22

* mean±sd (min to max)

Spherical equivalent (se) and the increment of spherical equivalent (dse) at different time points were summarized in Table 2-1a and Table 2-1b respectively.

Table 2-1a indicated that mean spherical equivalents were different statistically between MIT and non-MIT group since 0.5 year till 5 years later.

Table 2-1a Summary statistics of mean spherical equivalent (se) at different time points

Time of follow-up (year)	MIT (n=364), se	Non-MIT (n=174), se	p-value
At recruitment *	-0.81±0.43	-0.87±0.58	P=0.1381
Year 0.5*	-0.98±0.52	-1.13±0.67	P=0.0043
Year 1*	-1.15±0.63	-1.39±0.76	P=0.0000
Year 2*	-1.46±0.80	-2.01±0.99	P=0.0000
Year 3*	-1.75±0.97	-2.58±1.12	P=0.0000
Year 4*	-2.10±1.15	-3.30±1.26	P=0.0000
Year 5*	-2.50±1.30	-4.12±1.36	P=0.0000

* mean±sd, se: spherical equivalent, p-value < 0.05 for statistical significance

After 5-year follow-up, mean myopia progression (dse) was 1.69 ±1.06 D and 3.24±1.08 D in MIT and non-MIT group (P=0.0000) respectively (Table 2-1b). Table 2-1b also indicated that mean myopia progressions were different statistically between MIT and non-MIT group since 0.5 year till 5 years later.

Table 2-1b Summary statistics of spherical equivalent increment (dse) at different time points

Time of follow-up (year)	MIT (n=364), dse	non-MIT (n=174), dse	p-value
Year 0.5*	0.17±0.21	0.26±0.25	P=0.0000
Year 1*	0.34±0.32	0.51±0.39	P=0.0000
Year 2*	0.66±0.52	1.13±0.69	P=0.0000
Year 3*	0.94±0.70	1.71±0.82	P=0.0000
Year 4*	1.30±0.90	2.43±0.98	P=0.0000
Year 5*	1.69±1.06	3.24±1.08	P=0.0000

* mean±sd, dse: spherical equivalent increment (myopia progression), p-value < 0.05 for statistical significance

The results of the correlations of spherical equivalent (se) and the increment of spherical equivalent (dse) in Table 2-2a and Table 2-2b indicated that the longer the follow-up the lower the correlation for all schoolchildren.

Table 2-2a Repeated measure correlation of spherical equivalent (se) in MIT and Non-MIT group

	se0	se5	se10	se15	se20	se25	se30	se35	se40	se45	se50
se0	1.0000										
	1.0000										
se5	0.9211	1.0000									
	0.9328	*1.0000*									
se10	0.8819	0.9380	1.0000								
	0.8667	*0.9424*	*1.0000*								
se15	0.8393	0.9100	0.9497	1.0000							
	0.7976	*0.8871*	*0.9582*	*1.0000*							
se20	0.8032	0.8782	0.9078	0.9610	1.0000						
	0.7325	*0.8201*	*0.9126*	*0.9674*	*1.0000*						
se25	0.7833	0.8567	0.8925	0.9445	0.9713	1.0000					
	0.7050	*0.7978*	*0.8808*	*0.9283*	*0.9672*	*1.0000*					
se30	0.7616	0.8353	0.8718	0.9282	0.9490	0.9718	1.0000				
	0.7065	*0.7795*	*0.8463*	*0.8961*	*0.9345*	*0.9626*	*1.0000*				
se35	0.7343	0.8141	0.8447	0.9052	0.9393	0.9627	0.9752	1.0000			
	0.6867	*0.7508*	*0.8211*	*0.8637*	*0.9081*	*0.9417*	*0.9833*	*1.0000*			
se40	0.7135	0.7948	0.8226	0.8830	0.9160	0.9412	0.9605	0.9833	1.0000		
	0.6624	*0.7170*	*0.7891*	*0.8298*	*0.8804*	*0.9225*	*0.9618*	*0.9835*	*1.0000*		
se45	0.6891	0.7637	0.7921	0.8492	0.8819	0.9095	0.9255	0.9561	0.9715	1.0000	
	0.6463	*0.6872*	*0.7576*	*0.7993*	*0.8570*	*0.9049*	*0.9447*	*0.9662*	*0.9847*	*1.0000*	
se50	0.6792	0.7576	0.7810	0.8351	0.8747	0.9030	0.9165	0.9493	0.9649	0.9893	1.0000
	0.6448	*0.6852*	*0.7543*	*0.7958*	*0.8488*	*0.8942*	*0.9299*	*0.9487*	*0.9697*	*0.9875*	*1.0000*

MIT: n=364, *Non-MIT: n=174*

Table 2-2b Repeated measure correlation of spherical equivalent increment (dse) in MIT and Non-MIT group

	dse5	dse10	dse15	dse20	dse25	dse30	dse35	dse40	dse45	dse50
dse5	1.0000									
	1.0000									
dse10	0.7095	1.0000								
	0.7544	*1.0000*								
dse15	0.6761	0.8449	1.0000							
	0.6718	*0.8921*	*1.0000*							
dse20	0.6313	0.7563	0.9037	1.0000						
	0.5747	*0.8254*	*0.9359*	*1.0000*						
dse25	0.5980	0.7399	0.8737	0.9371	1.0000					
	0.5652	*0.7718*	*0.8616*	*0.9362*	*1.0000*					
dse30	0.5735	0.7138	0.8497	0.8961	0.9446	1.0000				
	0.4965	*0.6791*	*0.7907*	*0.8712*	*0.9275*	*1.0000*				
dse35	0.5654	0.6814	0.8186	0.8885	0.9340	0.9564	1.0000			
	0.4477	*0.6416*	*0.7355*	*0.8268*	*0.8914*	*0.9703*	*1.0000*			
dse40	0.5508	0.6556	0.7881	0.8534	0.9011	0.9345	0.9726	1.0000		
	0.3970	*0.5966*	*0.6853*	*0.7856*	*0.8627*	*0.9359*	*0.9727*	*1.0000*		
dse45	0.5090	0.6152	0.7382	0.8023	0.8535	0.8806	0.9307	0.9550	1.0000	
	0.3392	*0.5427*	*0.6372*	*0.7509*	*0.8372*	*0.9100*	*0.9455*	*0.9754*	*1.0000*	
dse50	0.5138	0.6052	0.7195	0.7964	0.8481	0.8700	0.9226	0.9464	0.9836	1.0000
	0.3385	*0.538*	*0.6326*	*0.737*	*0.8185*	*0.8853*	*0.9166*	*0.9512*	*0.9799*	*1.0000*

MIT: n=364, *Non-MIT: n=174*

Mean spherical equivalents of myopia (se) over 5-year period were shown in Figure 2-1, in which myopia progression in non-MIT group appeared faster than that in MIT group.

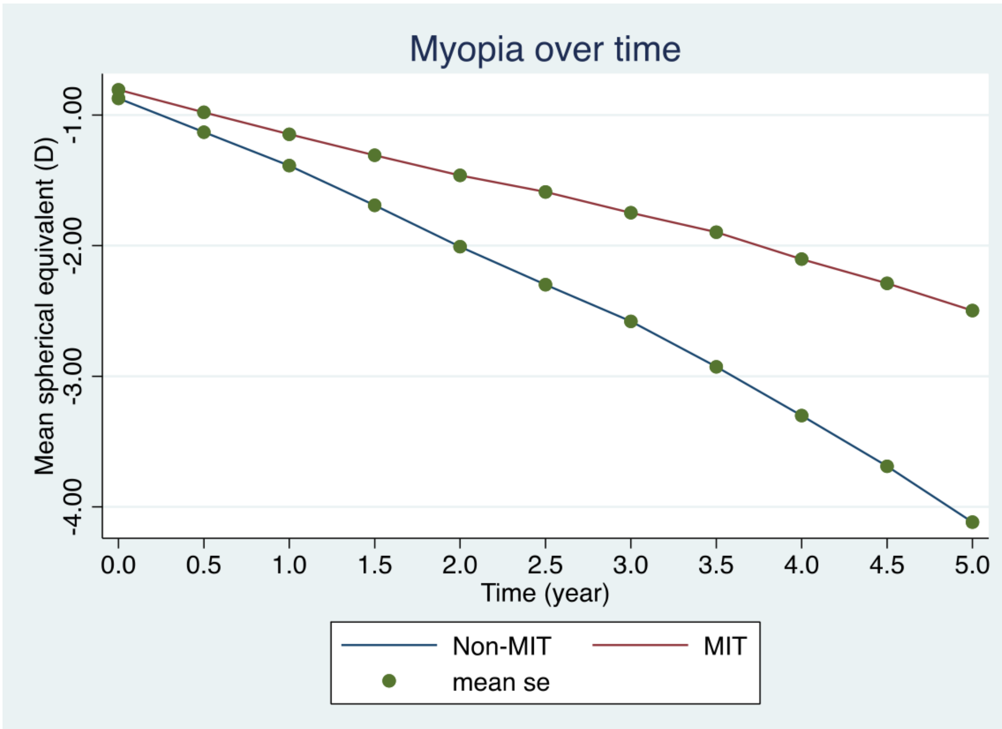


Figure 2-1 Spherical equivalents (se) over time

Axial length (al) and the axial length elongation (dal) at different time points were summarized in Table 2-3a and Table 2-3b respectively. Table 2-3a indicated that mean axial lengths were different statistically since 2.5 years till 5 years later.

Table 2-3a Summary statistics of axial lengths at different time points

Time of follow-up (year)	MIT (n=364), al	non-MIT (n=174), al	p-value
At recruitment *	23.48±0.54	23.45±0.70	P=0.5973
Year 1*	23.63±0.57	23.66±0.75	P=0.6458
Year 2*	23.78±0.58	23.87±0.78	P=0.1099
Year 2.5*	23.84±0.59	23.99±0.80	P=0.0147
Year 3*	23.91±0.60	24.10±0.80	P=0.0018
Year 4*	24.08±0.60	24.32±0.81	P=0.0001
Year 5*	24.23±0.63	24.59±0.86	P=0.0000

* mean±sd, al: axial length

Table 2-3b indicated that mean axial elongation were different statistically starting from 0.5 years till 5 years later. After 5-year follow-up, mean axial elongation was 0.67±0.30 mm and 1.01±0.44 mm in MIT and non-MIT group (P=0.0000), respectively.

Table 2-3b Summary statistics of axial elongation (dal) at different time points

Time of follow-up (year)	MIT (n=364), dal	Non-MIT (n=174), dal	p-value
Year 0.5*	0.075±0.09	0.10±0.108	P=0.0015
Year 1*	0.15±0.12	0.20±0.13	P=0.0000
Year 2*	0.30±0.17	0.42±0.27	P=0.0000
Year 3*	0.43±0.22	0.66±0.35	P=0.0000
Year 4*	0.60±0.26	0.87±0.41	P=0.0000
Year 5*	0.67±0.30	1.01±0.44	P=0.0000

*mean±sd, axial elongation (dal): axial length increment = al (time t) – al (t = 0)

Axial length (al) and axial elongation (dal) for both groups over time were illustrated in Figure 2-2a and Figure 2-2b. Mean axial length was longer in MIT group at recruitment (time 0) but surpassed by non-MIT group 0.5 year later (Figure 2-2a) and the differences between two groups enlarged afterwards (Figure 2-2a and Figure 2-2b).

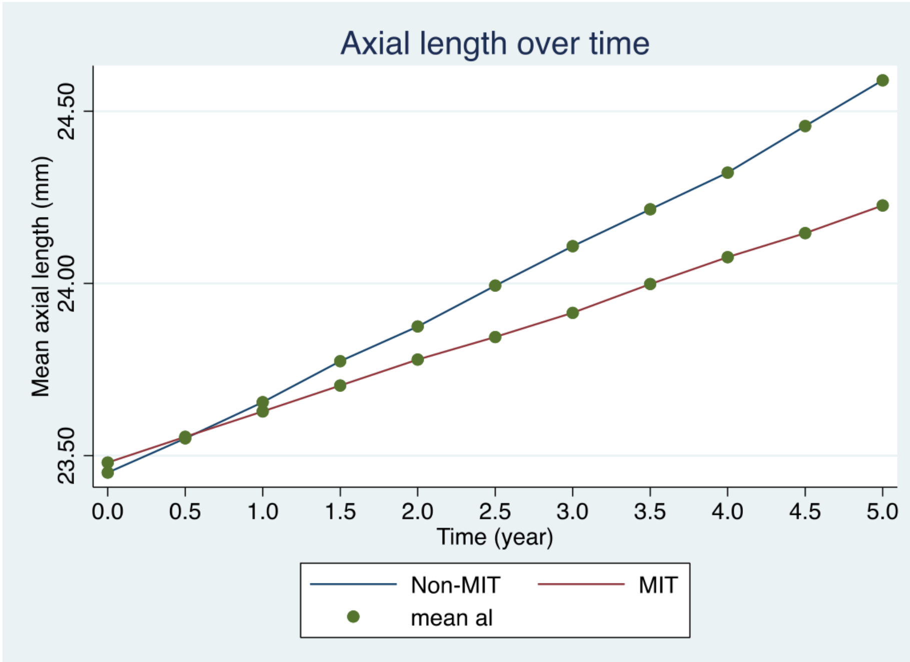


Figure 2-2a Axial lengths (al) over time

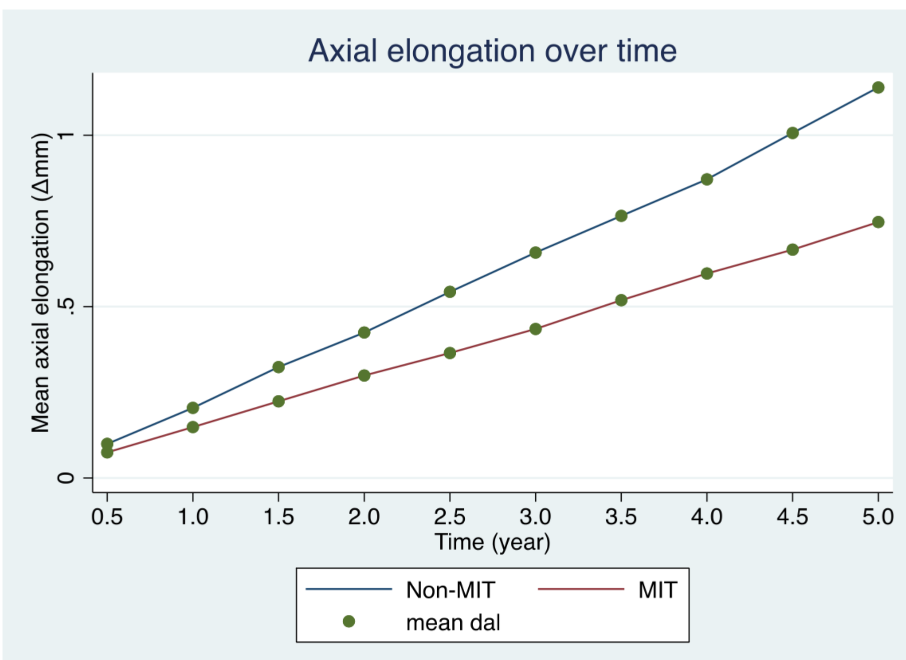


Figure 2-2b Axial length elongation (dal) over time

Generalized Estimating Equations Analysis (GEE) for Cross Sectional Relationship between spherical equivalents and axial lengths

Spherical equivalent (se) versus axial length (al) and myopia progression (dse) versus axial length elongation (dal) in Figure 2-3a, and Figure 2-3b indicated the positive correlation for both non-MIT and MIT groups. The results in Figure 2-3a revealed that myopia progressed as 0.97 D in MIT group more than 0.88 D in non-MIT group per 1mm axial length elongated after adjusting for age, gender and parents' myopia.

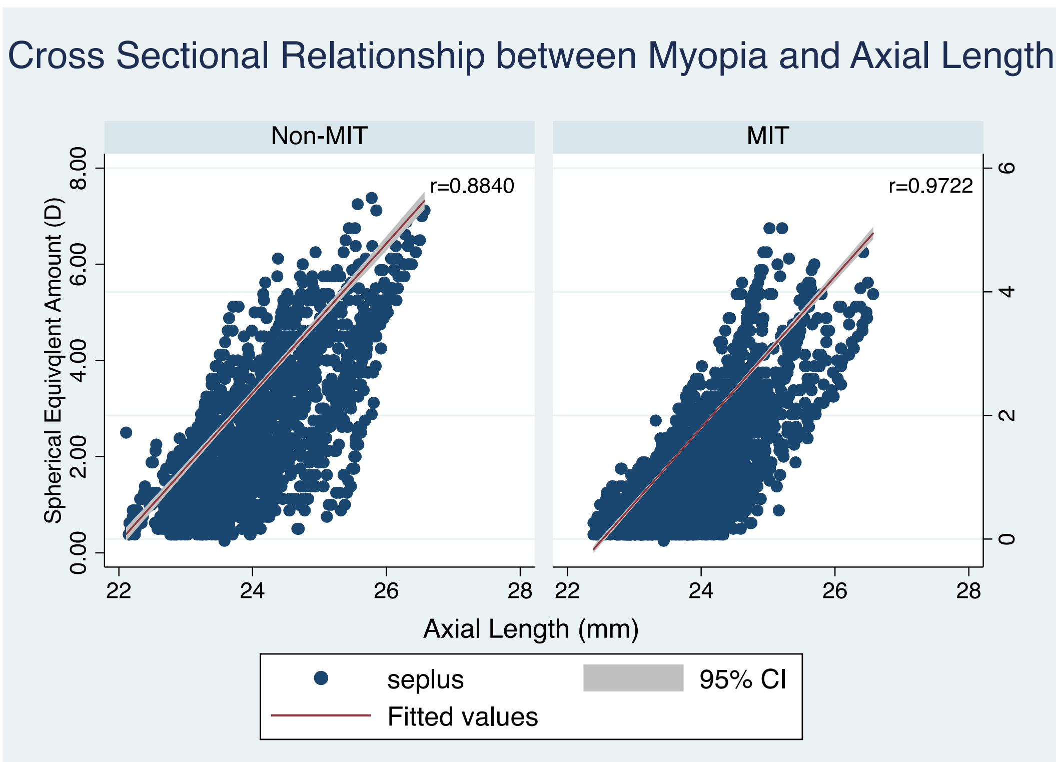


Figure 2-3a Myopia (se) vs. axial length (al) with a fitted line

Compared to baseline data, myopia progression (dse) and axial elongation (dal) were used to analyze the cross sectional relationship. The results in Figure 2-3b indicated that myopia progressed as 1.44 D in non-MIT group more than 1.06 D in MIT group per 1mm axial length elongating after age and parents' myopia adjusted.

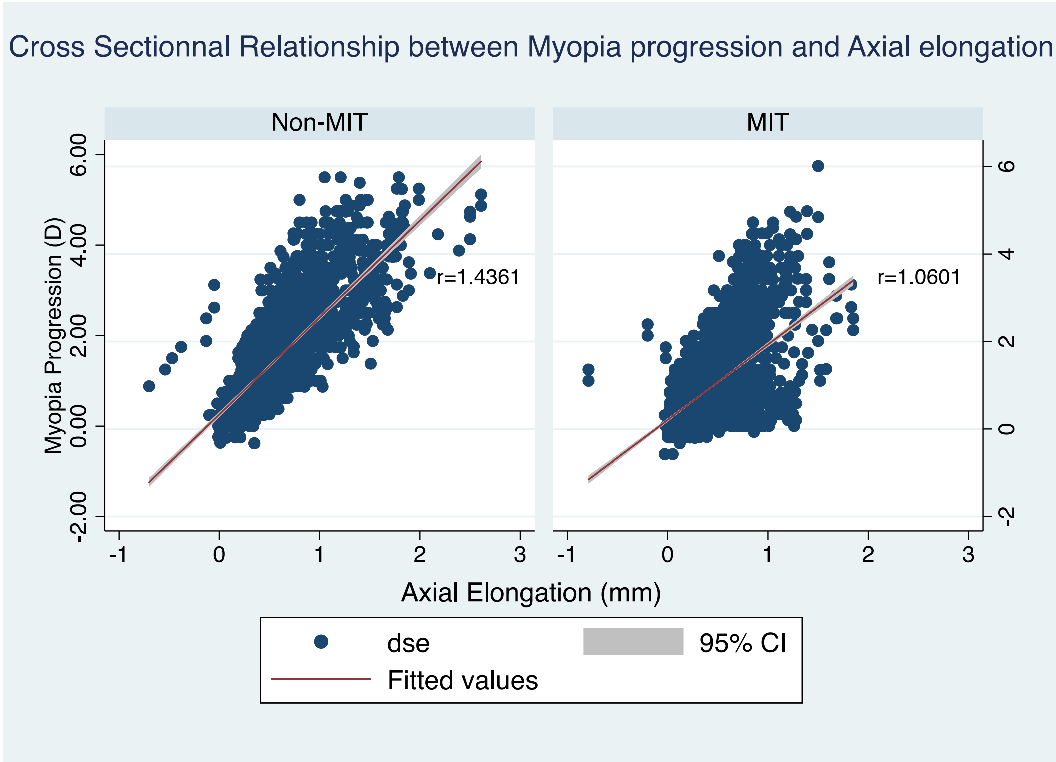


Figure 2-3b Myopia progression (dse) vs. axial elongation (dal) with a fitted line

Repeated measures mixed model

We substituted “se” as “seplus” for the amount of spherical equivalent (seplus = -se) in analysis for better illustrating the results.

Joint test

Joint test in Table 2-4 indicated that the treatment (MIT) by time interaction and main effects (MIT) were significant.

Table 2-4 Joint tests of the interaction and main effects

	df	chi2	P>chi2
seplus			
MIT	1	84.63	0
time	10	17352.73	0
MIT#time	10	1828.27	0

Linear growth model

Simple slopes

Time was treated as a continuous variable (ctime) in Linear growth model. The results in Table 2-5a indicated that the slope of non-MIT group was almost twice that of MIT group. Mean yearly myopia progression was 0.33±0.004 D/y and 0.64 ±0.006 D/y in MIT and non-MIT group (P=0.000), respectively (Figure 2-4a).

Table 2-5a The slopes of spherical equivalents in MIT and non-MIT groups

	dy/dx	Delta-method Std. Err.	z	P> |z|	[95% Conf.	Interval]
ctime						
Non-MIT	0.0640642	0.0006094	105.12	0	0.0628697	0.0652586
MIT	0.0327627	0.0004213	77.76	0	0.0319369	0.0335885

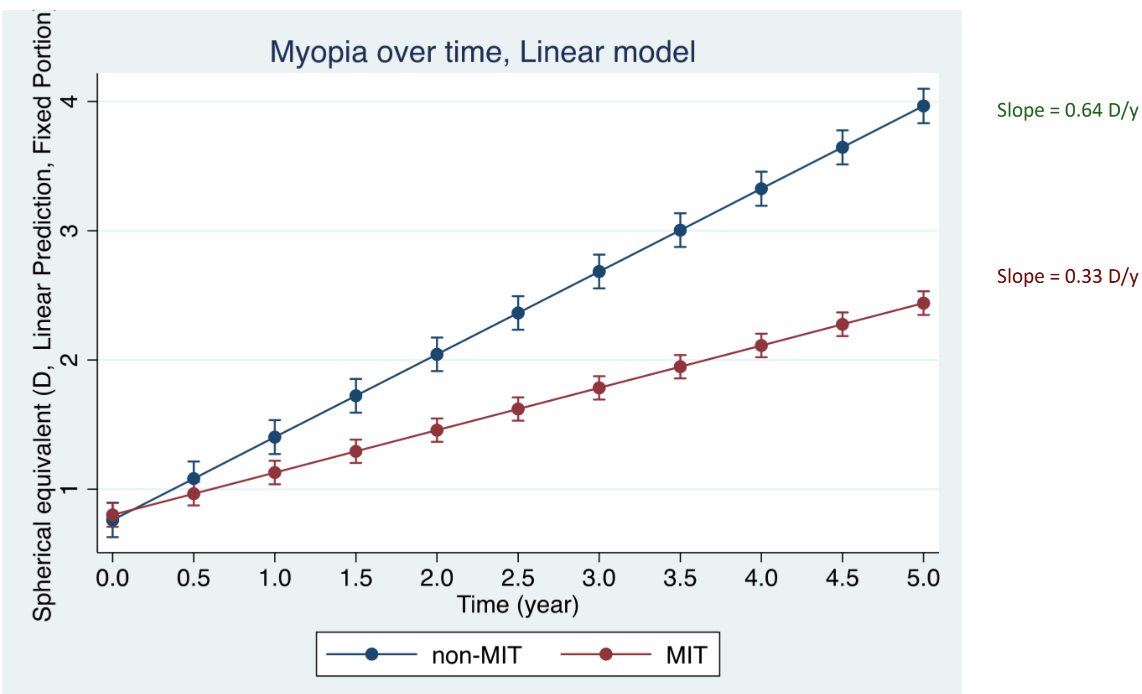


Figure 2-4a Spherical equivalent (se) over time (adjusted prediction with 95%CIs), linear effect

The results in Table 2-5b indicated that the slope of non-MIT group was almost 1.5 times that of MIT group. Mean axial elongation was 0.15±0.001 D/y and 0.23 ±0.002 D/y in MIT and non-MIT group (P=0.000), respectively (Figure 2-4b).

Table 2-5b The slopes of axial length (al) in MIT and non-MIT groups

	Delta-method					
	dy/dx	Std. Err.	z	P> |z|	[95% Conf.	Interval]
ctime						
Non-MIT	0.0226171	0.0002228	101.53	0	0.0221805	0.0230538
MIT	0.0148509	0.000154	96.42	0	0.0145491	0.0151528

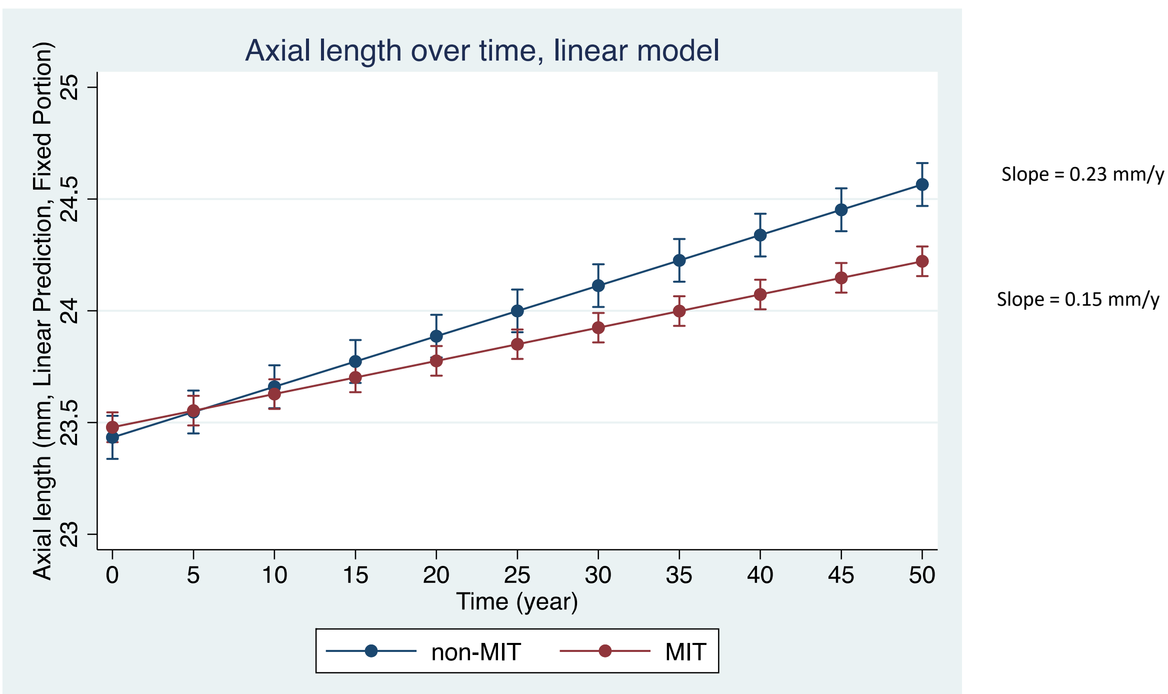


Figure 2-4b Axial length (al) over time (adjusted prediction with 95%CIs), linear effect

Discussion

Myopia is the public health issue causing attention globally; the situation in East Asia is most serious (Harb & Wildsoet, 2019; Prousali et al., 2019). In Taiwan, myopia prevalence of primary schoolchildren is the second highest worldwide which progressed around 1.0 - 1.2D each year if only wearing glasses without any other treatment (Chang, 1999; HPA, 2018; Liou, 2019). Myopia, especially high myopia, started in the childhood has high possibility to be a heavy social health and economic burden eventually (Bourke et al., 2019).

The traditional high concentration (1.0%) atropine eye drops was most effective but caused difficulties with near work and severe photophobia for outdoor activities (Han, W. T., Rong, & Xu, 2019; Tran et al., 2018). Even OK lenses, even costly and having corneal side effects, are used alone (Cho & Cheung, 2012)or combined with atropine (Chen et al., 2019; Sun et al., 2015; Tan, Ng, Cheng, Woo, & Cho, 2019) to delay myopia progression. The new trial of low concentration (0.01%, 0.025%, 0.05%) atropine revealed some kind of dose-dependent efficacy (Tran et al., 2018; Yam et al., 2019)the data were suspicious of lack of evidence-based support (Brennan & Cheng, 2019). The multifocal spectacles existed the waning effect to reduce myopia progression over long-term follow-up (Brennan & Cheng, 2019; Holden, B. et al., 2014; Kaphle, Atchison, & Schmid, 2019). Among all the methods trying to inhibit or slow down the progression of myopia, atropine eye drops are the most friendly, economic and reliable treatments. We use medium-concentration atropine (0.125%, 0.25%, 0.5%) eye drops based on sunlight intensity in different seasons, trying to reduce the side effects of photophobia and near-work activity, to delay myopia progression in primary schoolchildren.

Taiwan is located at subtropical zone with Tropic of Cancer passing through Chiayi County. Spring is warm with moderate sunlight, summer is hot and humid with strong sunlight, autumn is cool with moderate sunlight, and winter is windy and a little cold with weak sunlight.

We thus recommend 0.125% atropine eyedrops used in summer, 0.25% atropine eyedrops used in spring and autumn, and 0.5% atropine eyedrops used in winter for those schoolchildren having myopia more than -1.00D. However, for those having myopia less than -0.75D, the concentrations would be adjusted on the bases of clinical and daily responses, instead of only seasonal concern, from schoolchildren at follow-up visits.

There are evidences showing apparent familial aggregation, and genetic factors contribute to the pathogenesis of myopia, especially high myopia (Cai et al., 2019; Mutti, Mitchell, Moeschberger, Jones, & Zadnik, 2002); several candidate myopia genes have been identified by gene-based analyses (Flitcroft et al., 2018). Environmental influences and gene-environment interactions get more attention to explain the myopiagenesis (Harb & Wildsoet, 2019; Miraldi Utz, 2017; Morgan & Rose, 2019; Tedja et al., 2019; Vishweswaraiah et al., 2019)Urbanization, educational pressure with intensive reading and near-work activities, too long indoor activities and insufficient outdoor time with sunlight exposure (Cao, K., Wan, Yusufu, & Wang, 2019; Guggenheim et al., 2012;

Morgan & Rose, 2019; Shapira et al., 2019), poor eating habitats with nutrients imbalance are the common environmental risk factors. Heredity is the factor that we can not change; hence medical and environmental interventions remain the main strategies to inhibit myopia progression in this century. We emphasize on healthy life styles with “853240” daily implementation in additional to atropine eye drops treatment.

After 5-year follow-up, mean myopia progression was 1.69 ±1.06 D and 3.24±1.08 D in MIT and non-MIT group (P=0.0000), respectively (Table 2-1b); and mean yearly myopia progression was 0.33±0.0004 D and 0.64 ±0.0006 D in MIT and non-MIT group (P=0.000), respectively (Table 2-5a).

Magnetic Resonance Imaging (MRI) study has found that myopic eyes were much larger in all 3 dimensions, especially in length; thus eye shape could possibly be considered as a myopia biomarker. Most high myopic eyes owned a pointed shape compared to the blunt shape of emmetropic eyes (Matsumura, Kuo, & Saw, 2019). The eye shape change could be explained by the point of view of anatomy. The anterior face of eye globe was the only part not confined by bony structures, thus eye protruded anteriorly more easily and changed the shape from basketball to soccer while myopia progressed. Axial elongation with myopia progression elucidated the pathologic change accompanied with abnormal eye shapes and biomechanical stretching.

The axial elongation differed significantly since 0.5-year till 5-year follow-ups. The axial elongations were 0.075±0.09 mm and 0.10±0.108 mm in MIT and non-MIT group (P=0.0015) at 0.5-year follow-up; 0.67±0.30 mm and 1.01±0.44 mm in MIT and non-MIT group (P=0.0000) at 5-year follow-up, respectively (Table 2-3b). Myopia progressed as 1.44 ±0.04D /mm in non-MIT group more than 1.06 ±0.05D /mm in MIT group (Figure 2-3b). The results above indicated the worse the myopia, the longer the eye globe.

The mixed-effects models we used are more flexible and have more advantages than disadvantages (UCLA, 08042019) as listed below.

Advantages	Disadvantages
• Computing correct standard errors for each effect automatically • Allowing unbalance or missing observations within-subject • Allowing unequal time intervals • Allowing various within-subject covariance structures • Allowing time to be treated as categorical or continuous	• xtmixed reporting results as chi-square; the p-values are appropriate for large samples and are biased downwards in small samples

These findings of the study suggest that medium-concentration (0.125%, 0.25% and 0.5%) atropine modified seasonally and healthy lifestyle “853240” interventions at school and home may play an important role in delaying myopia progression for primary schoolchildren. This health issue warrants consideration of public prevention strategies and further investigation in a big data set for generalization.

Limitations and Strengths

The strength of this study is that our data were from a metropolitan citywide database that produced data prospectively. The scale of this database was big to recruit all local public primary school students from all districts except several private school or international schools, such as Taipei American School and Taipei European School. Those who were not recruited in MIT program served as control group. A 5-year longitudinal follow-up, from 2nd grade to 6th grade, provided a chance to evaluate the long-term effect of myopia control. The association between myopia progression and atropine or OK lens has been studied deeply in the past. However, MIT program is a new intervention and focus on the modification of schoolchildren daily life (Hsu et al., 2016). With the healthy interventions, we may arise the public awareness in preventing myopia. Nonetheless, there are several limitations in this study. First, this is a retrospective cohort study. We cannot exclude the presence of undetected bias. The cases we used for analyses might come from highly educated parents because my clinic is located in the Science Park, comparable to Silicon Valley in California USA, where the headquarters of high-tech industries including nVDIA, Foxconn, MediaTech etc. are located. Second, there are some potential confounders not assessed, such as compliance to MIT program or to medication (atropine) and use of other alternative regimens including acupuncture. Even some unmeasured confounding factors cannot be eliminated completely; we attempt to minimize selection bias by adjusting all obtainable demographics and comorbidities. Third, the atropine concentrations are not recorded clearly in the claims database. Forth, the difference of lifestyle and education pressure between urban and rural limited the ability of generalization from this study. Fifth, the scheduled frequency of eye clinic exam for only twice a year is not enough to keep effective treatment for those who did not spend more time to visit the clinic. Finally, the regular daily activities were considered in Twn VFQ-25 to fit children that might affect the score of some subdomains.

Long-term treatment and follow-up, especially observing pubertal effects on eye shape change and/or axial elongation, till finishing high school should be considered for future study.

Chapter 3

Cost-effectiveness Analysis for the Five-year MIT Program of Myopia Control in Taipei Primary School Students

Abstract

Purpose

To evaluate the cost-effectiveness of modified atropine eye drops for slowing myopia progression between MIT (Myopia Intervention Study in Taipei) and non-MIT group.

Design

A prospective study. Atropine eye drops with modified concentrations and daily life interventions used for schoolchildren in MIT program and schoolchildren in non-MIT program served as controls.

Participants

All second-grade schoolchildren from the public primary schools in Taipei City willing to join MIT program were recruited in September 2013 as study candidates. Students from non-MIT group served as controls. The schoolchildren in MIT group carrying a “Vision Protection Passport” attached with the intervention tips had the privilege to get free ocular examination and vision test.

MIT students were followed up every one to two months for continuing atropine therapy, however non-MIT students visited ophthalmic clinic every semester or 6 months only for finishing the “Vision Exam Sheet” required by the Ministry of Education. Enrollment criteria included the both eyes having at least spherical equivalent of at least -0.25 diopters (D), astigmatism power no more than 2.0 D and corrected vision as 1.0 (20/20). Students with previous ocular injury, amblyopia, cataract, keratoconus, myopia over -10.0D, ocular hypertension, glaucoma or OK (orthokeratology) lens user were excluded. The subjects who has completed all ocular examinations and vision tests every 6 months, continued using atropine eye drops and followed up for five years till they graduated from the primary school at sixth grade in June 2018 were recruited in this study. Three hundred and sixty four subjects were included in MIT (n = 364) group compared to 174 subjects counted in non-MIT (n = 174) group.

Methods

0.1%, 0.25%, or 0.5% atropine eye drops were used in MIT groups modified with seasonal sunlight intensity and severity of myopia. Anti-UV sunglasses were prescribed for subjects who had outdoor activities and progressive spectacles were given for children who had difficulty in school learning. Multifactorial interventions of “853240” were used in MIT program to enhance and improve the effects of atropine eye drops. “8” or sleeping 8 hours; “5” for eating 5-kind of colorful vegetables and fruits; “3” for sitting with 3 ninety angles (ankle, knee and hip); “2” for doing 2-hr outdoor activities; “4” for using 4 3Cs (TV, iPad, computer, cell phone) as less as possible; “0” for taking 10–minute rest every 30-minute eye use. Biometrical parameters including refractive error, uncorrected and corrected visual acuity, intraocular pressure (IOP), and axial length were measured under cycloplegic condition per six months with follow-ups for 5 years. The cost of NTD 400 sponsored by MIT program would be reimbursed to all contracted department of ophthalmology at hospitals or private ophthalmic clinics by the Department of Health, Taipei City Government (TCHIRB-1020501) every 6 months for the first 3 years and then yearly afterwards till students’ graduation from the primary school. All secondary data were retrieved from schoolchildren of MIT and non-MIT group at Harvard Vision Center. Costs composing of the reimbursement from governments, the out-of-pocket co-payments, school fee loss, cares’ wage loss and extra costs were recorded for both groups. The effectiveness was defined as the increments of spherical equivalents (dse) for myopia progression. The incremental cost effectiveness ratios (ICERs) were calculated as the difference in cost divided by the difference in effectiveness comparing MIT and non-MIT groups. Incremental net benefits (INBs = $\lambda(\text{Effect}_{\text{MIT}} - \text{Effect}_{\text{non-MIT}}) - (\text{Cost}_{\text{MIT}} - \text{Cost}_{\text{non-MIT}})$) were also compared between both groups under different willing-to-pay (w2p) amounts. Because the more dse the worse response, we thus put “detr “ for detrimental response” in heabs regression, and defined ICER = $(\text{Cost}_{\text{MIT}} - \text{Cost}_{\text{non-MIT}}) / (\text{Effect}_{\text{non-MIT}} - \text{Effect}_{\text{MIT}})$.   The 95% confidence intervals and ellipses for ICERs were estimated through bootstrapping and heapbs module analysis.

Main Outcome Measures

Costs and effectiveness (myopia progressions).

Results

Refractive data were available for 538 participants consisting of 364 students from MIT group (n = 364) and 174 students from non-MIT group (n = 174). The basic demographic characteristics, including age, gender, and parents' myopia status, showed no statistic significances at recruitment (year 0). The effectiveness, defined as the increments of spherical equivalents (dse) compared to baseline (year 0), calculated for year 0.5 (dse5) were 0.17±0.21D and 0.26±0.25D; for year 1.0 were 0.34±0.32D and 0.51±0.39D; for year 2.0 were 0.66±0.52D and 1.13±0.69D; for year 3.0 were 0.94±0.70D and 1.71±0.82D; for year 4.0 were 1.30±0.90D and 2.43±0.98D; for year 5.0 were 1.69±1.06D and 3.24±1.08D in the MIT and non-MIT groups respectively. The ICERs were revealed as follows: 1837.305, 1830.469, 1344.325, 1282.426, 611.951 and 253.602 for year 0.5, year 1.0, year 2.0, year 3.0, year 4.0 and year 5.0 respectively. The INBs under w2p (1000) were listed as follows: -72.078, -144.004, -165.110 and -216.257 at year 0.5, year 1.0, year 2.0 and year 3.0 respectively; however, INB turned to be positive as 439.099 at year 4.0 and climbed up to 1159.578 at year 5.0. INB at year 3.0 having the lowest value, like a valley bottom, indicated a healthy turning point for reasonable investment; ICER was noted to decline from 1282.426 to 611.951 and then to 253.602 for the following two years.

Conclusions

The results of low ICER and high INB at year 4.0 and 5.0 suggest a promising future for carrying on MIT program to a longer future with broader participation for school-aged children.

Introduction

The importance of myopia

Myopia is the most common ocular disorder with a potential danger of blindness thus recognized as the leading cause of visual impairment worldwide; however, it is overlooked most of time and there is no really safe level or cure of myopia (Bourke et al., 2019; Miraldi Utz, 2016; NIH, 2010). Myopic eye seems larger than normal (Matsumura et al., 2019)and even larger in pathological high myopia eye. The abnormal growth leads to an extreme extent thus makes it prone to retinal tears, holes, hemorrhages, and even detachment (NIH, 2010). Myopia based on the severity is classified into three degrees as low myopia (less than 3.00 D), medium myopia (3.00 to 6.00 D), and high myopia (greater than 6.00 D). Development of myopia could be divided into four stages of life: (1) congenital myopia is diagnosed at birth and persists through infancy, (2) youth-onset occurs in children less than 20 years of age, (3) early adult-onset of myopia occurs in individuals less than 40 years of age and (4) late adult-onset of myopia is diagnosed among those older than 40 years of age (Goss et al., 2006)

A report from World Health Organization (WHO) estimated that 153 million people worldwide had visual impairment due to uncorrected refractive error (Kuang et al., 2016). Holden revealed that 22.9% of the world population or 1.4 billion individuals are myopic, and high myopic people in year 2000 are 63 million persons or 2.7% of the world population (Holden, B. A. et al., 2016). Growing prevalence and severe comorbidities associated with myopia make it a worrisome vision disorder. High myopia is associated with retinal degeneration, macular hemorrhage, glaucoma, cataract, visual impairment and even blindness (Holden, Brien, 2017; Huang, Chang, & Wu, 2015). Incidence of myopia is rising and the prevalence of myopia in the US has increased from 25% to 44% in the last 30 years (Miraldi Utz, 2016). The prevalence of myopia in Asian countries can be as high as 80% among young adult populations (Miraldi Utz, 2016). By year 2020, the prevalence of myopia is expected to be about 2.5 billion persons (Miraldi Utz, 2016). Holden predicted that by year 2050, there is going to be 4.95 billion, almost doubled Utz's estimates for year 2020, or 52.0% of the world population getting myopia as revealed Figure 1-1, Chapter 1 and almost 0.925 billion people or 10.0% of the world population having high myopia as shown in Figure 1-2 , Chapter 1 (Holden, B. A. et al., 2016).

Several studies emphasize that urbanization and increased academic pressures contribute to the rising prevalence of myopia (Huang et al., 2015; Shapira et al., 2019). Near work, which is defined as activities done at short distance from the eye such as reading, studying, writing, using computers, playing video games, and watching TV, is one of the most important environmental risk factors for myopia. (Huang et al., 2015). Studies have shown that myopic children spend more time on reading compared to non-myopic children, with no significant differences in studying, using a computer, or watching TV. Thus, reading is hypothesized to be the main near work activity associated with myopia (Huang et al., 2015). Myopia develops and progresses most among schoolchildren, the term “school myopia” perhaps was coined as a result of near work behaviors (Chua et al., 2016; Huang et al., 2015; Miraldi Utz, 2016).

“School myopia” is the most common type of non-pathologic myopia diagnosed among school-aged children (Miraldi Utz, 2016). Myopia usually develops around the age of six to eight years and progresses through the age of 15 or 16 years at rate of 0.50 diopters (D) per year in Western children and 1.00 D in Asian children (Huang et al., 2015; Liou, 2019; Lu, P. C. & Chen, 2010). Other reports have confirmed that myopia among Asian children can progress twice faster than Western children (Huang et al., 2015). This phenomenon can be explained by differences in educational systems, on academic pressure, and impacts on spending more time on near works in eastern countries compared to focusing on physical education and spending more time on outdoor activities and sports in western countries (Huang et al., 2015). Spending extra hours after school on near activities is hypothesized to worsen myopia progression among Asian children (Huang et al., 2015; Mutti et al., 2002; Saw et al., 2000; Saxena et al., 2015).

Simple myopia in children and adults are the most common among various types of myopia. Pseudomyopia among most schoolchildren results from increased ocular refractive power due to overstimulation of the eye, especially near works. Pathological myopia, also known as degenerative myopia, is a high degree of myopia with severe degenerations over the posterior pole of the eye. (Goss et al., 2006).

Beside the economic and psychosocial implications, myopia also increases the risk for comorbidities such as myopic choroidoretinal neovascularization and degeneration, myopic retinoschisis and even retinal detachment and decreases quality of life (Bourke et al., 2019; Miraldi Utz, 2016). Study has shown that participants over the age of 54 with levels of myopia ranging from -6 to -10 diopters (D) had an odds ratio of 3.4 as a lifetime risk for visual impairment; the odds ratio was even as high as 22 for those with myopia levels greater than -10 D (Miraldi Utz, 2016). To address these concerns, the Vision 2020 initiative by WHO listed myopia as one of the top five immediate priorities (Huang et al., 2015).

Risk Factors of Myopia

Both genetic and environmental risk factors contribute to myopia. Several studies have shown that myopia progresses faster when it develops at younger age, and that early-onset myopia is associated with high myopia later in life (Chua et al., 2016; Wu, Tsai, Wu, Yang, & Kuo, 2013). A major risk factor for progression of myopia among older children and adolescents is axial elongation of the posterior segment (Lee, M. W., Lee, Lim, & Kim, 2019; Lu, P. C. & Chen, 2010; Matsumura et al., 2019; Miraldi Utz, 2016). Changes in the axial length and refractive power of the eye leading to emmetropia or low-grade hypermetropia are caused by emmetropization, which involves a complicated array of vision-driven retinal signaling (Miraldi Utz, 2016). Matsumura used MRI and AI techniques to demonstrate that myopic eyes are larger with longer axial lengths than ocular height and width (Matsumura et al., 2019). This phenomenon is hypostasized as signaling cascades in the retina followed by a choroidal response with scleral matrix remodeling. Experimental studies have induced myopia in animals through placing a minus lens during early development to alter the visual experience-driven signaling cascades, thus causes hypermetropic defocus and myopic progression (Miraldi Utz, 2016). Other risk factors include patient age, intraocular pressure, refractive powers of the cornea and lens, axial length, and aqueous and vitreous refractive indices, all of which contribute to the refractive state of the eye (Han, X. et al., 2018; Miraldi Utz, 2016). Genetic factors, such as susceptibility variants within any gene encoding proteins (Miraldi Utz, 2017) in these signaling cascades, do contributions to a myopic phenotype (Miraldi Utz, 2017; Stokman et al., 2016; Storm, Heegaard, Christensen, & Nielsen, 2014).

Myopia can also be categorized as syndromic or non-syndromic (Cai et al., 2019; Flitcroft et al., 2018; Miraldi Utz, 2016; Tedja et al., 2019; Vishweswaraiah et al., 2019). Syndromic myopia, defined as systemically inherited disease, tends to be inherited in a Mendelian fashion (Flitcroft et al., 2018; Miraldi Utz, 2017; Tedja et al., 2019). Non-syndromic myopia refers to myopia present in those who have a strong familial clustering of the trait but without other systemic traits (Miraldi Utz, 2016; Vishweswaraiah et al., 2019). The dramatic prevalence rise of “school myopia” in several regions of the world supports an environmental cause. (Miraldi Utz, 2016; Yotsukura et al., 2019) As the nature vs. nurture debate continues, there are more evidences revealing the gene-environment interactions at play in myopia progression. For example, children of myopia parents tend to spend more time in environments that increase the risk of myopia (Miraldi Utz, 2017; Morgan & Rose, 2019). One other evidence reveals retinal image and contrast processing, with a risk allele change, can lead to myopia in those who read intensely (Pozarickij, Williams, Hysi, Guggenheim, & UK Biobank Eye and Vision Consortium, 2019; Tang et al., 2019).

Several reports have revealed that natural light exposure in outdoor activities is preventative against myopia progression (Cao, K. et al., 2019; Guggenheim et al., 2012; Miraldi Utz, 2016). Lower rates of myopia occur in which behavioral and environmental risk factors are not present, such as rural areas where exposure to natural light is more common than in urban areas (Cao, K. et al., 2019; Miraldi Utz, 2016). On the contrary, higher levels of education and near works are associated with development of myopia (Miraldi Utz, 2016). In summary, age, genetics and parental status of refractive error, time spent outdoors and time spent doing near works are all suspected risk factors for myopia. Causal and associative relationships between risk factors and myopia in the literature are still not consistent thus more researches are needed to better understand heritability, gene-environment interactions, and other risk factors.

Myopia in Taiwan

Taiwan was coined the “the island of myopia” and “myopia capital of the world” in 1999. (Chang, 1999) Table 1-A and Table 1-B, Chapter 1 revealed myopia and high myopia prevalence of schoolchildren from year 1986 to year 2018 (HPA, 2018). The myopia prevalence of the sixth grade (63.3%) was 2.39 folds higher than the first grade (26.5%) in year 2018 (HPA, 2018). The myopia prevalence of preschool children, less than South Korea, and primary schoolchildren, less than Singapore, were both the second highest in the world; thus, Taiwan has won the fame as "the Kingdom of Myopia". (Liou, 2019)

Myopia Intervention in Taipei (MIT) program is sponsored by Taipei City Health Bureau and offers a free myopic status and ocular examination at contracted ophthalmic clinics or hospitals for the primary schoolchildren once or twice a year, besides, there are so called "853240" behavior modalities input to their day-to-day life activities by adjusting lifestyle (Enthoven et al., 2019; Rose, Morgan, Smith et al., 2008)and reducing risk factors and poor habits to enhance the effects of atropine eye drops.

The Health Care Index of Taiwan was ranked as No. 8 by NUMBEO (Wikipedia, 12/14/2019), a crowd-sourced global database of reported consumer prices, perceived crime rates, quality of health care, among other statistics, in year 2013, No. 2 in year 2018 and No. 1 since 2019 and keeps as Top 1 in year 2020 (NUMBEO, 02/02/2020) ; thus, cost-effectiveness should get more attention and emphasis than cost-saving only. There were studies discussing the dose-dependent efficacy of atropine (Tran et al., 2018)and socio-economic impact of myopia (Bourke et al., 2019); however, the cost-effectiveness of combined regimen of atropine eye drops with daily life interventions, such as MIT program, has not yet been established.

Methods

Inclusion and exclusion criteria

The second-grade schoolchildren from all public primary schools in Taipei City willing to join MIT program were recruited in September 2013 as study subjects. Schoolchildren from non-MIT group served as controls.

Inclusion criteria included:

(1) both eyes having spherical equivalent at least -0.25 D,

(2) astigmatism power no more than 2.0 D,

(3) the best corrected vision achieving 1.0 (20/20).

Exclusion criteria included:

(1) schoolchildren having previous ocular injury,

(2) amblyopia,

(3) cataract,

(4) keratoconus,

(5) myopia over -10.0D,

(6) ocular hypertension, and/or glaucoma,

(7) OK (orthokeratology) lens user.

All subjects recruited for this study have completed all ocular examinations and vision tests every 6 months and were followed up to five years till they graduated from the primary school at sixth grade in June 2018. There were 364 subjects in MIT (n = 364) group and 174 subjects in non-MIT (n = 174) group respectively.

Atropine eye drops

Atropine eye drops with three different concentrations of 0.1%, 0.25%, or 0.5% were used in MIT groups with seasonal modification according to the sunlight intensity and the severity of myopia. Anti-UV sunglasses were prescribed for subjects who had outdoor activities and progressive spectacles were given for children who had difficulty in reading, writing or near-works.

Interventions for MIT group

Multifactorial interventions of “853240” were used in MIT program to enhance and improve the effects of atropine eye drops. “8” stood for sleep at least 8 hours every night; “5” for eating 5-kind of colorful vegetables and fruits every day; “3” for sitting with 3 ninety angles (ankle, knee and hip); “2” for doing 2-hr outdoor activities every day; “4” for using 4 3Cs (TV, iPad, computer, cell phone) as less as possible; “0” for taking 10–minute rest every 30-minute eye use. There were no interventions used for non-MIT schoolchildren. Refractive error, uncorrected and corrected visual acuity, intraocular pressure (IOP), and axial length were measured under cycloplegic condition per six months with follow-ups for 5 years.

Costs

The schoolchildren in MIT group carrying a “Vision Protection Passport” attached with the intervention tips had the privilege to get free ocular examination and vision test. The cost of NTD 400 (USD 13.31), zero copayments, would be reimbursed to all contracted hospital ophthalmology departments or private ophthalmic clinics by the Taipei City Health Bureau every 6 months for the first 3 years and then yearly later on until graduation from the primary school. Schoolchildren in MIT group were followed up every one to two months for continuing atropine therapy, however schoolchildren in non-MIT group visited ophthalmic clinic every semester or 6 months only for finishing the “Vision Exam Sheet” required by the Ministry of Education. All schoolchildren would be prescribed atropine eye drops at follow-up visits, where the costs composed of NTD 457 (USD 15.21) paid by the Health Promotion Administration, Ministry of Health and Welfare as well as NTD 200 (USD 6.66) co-payments from their own pockets. Extra cost would cover some personal and travel expenses. Three percent was taken as annual discount rate. The currency exchange rate was 1 USD = 30.042 NTD. (Bank, 02222020)

Effectiveness

Spherical equivalents (se) at different time points were calculated. The increments of myopia progression (dse), se at time 0 minus se at time t, were recognized as effects. All secondary data were retrieved from schoolchildren in MIT and non-MIT groups at Harvard Vision Center. Cost-effectiveness was compared between MIT group (n = 364) and non-MIT groups (n = 174) using heabs and bootstrap model analysis (Gallacher, 02182020). Because response is “detr” (meaning a higher score of dse is detrimental), Incremental Cost Effectiveness Ratio (ICER) was defined and calculated as follows:

$$\text{ICER} = \frac{(\text{Cost}_{\text{MIT}} - \text{Cost}_{\text{non-MIT}})}{(\text{Effect}_{\text{non-MIT}} - \text{Effect}_{\text{MIT}})}$$

Incremental Net benefit (INB) is calculated as the following equation:

$$\text{INBs} = \lambda\ (\text{Effect}_{\text{MIT}} - \text{Effect}_{\text{non-MIT}}) - (\text{Cost}_{\text{MIT}} - \text{Cost}_{\text{non-MIT}})$$

Incremental net benefits (INBs) were also compared between both groups under different λ or willing-to-pay (w2p) amounts. Confidence ellipses and 95% CI for ICERs were estimated through bootstrapping and heapbs module analysis. Stata/IC 15.1 was applied for statistical analysis.

Results

The demographic characteristics in Table 3-1 indicated MIT and non-MIT group had compatible basic information and parameters.

Table 3-1 Demographic characteristics

At recruitment (time 0)	MIT	Non-MIT	p value
Spherical equivalent* (D)	-0.81±0.43 (-0.38 to -3.00)	-0.87±0.58 (-0.25 to -4.25)	P=0.14
Axial length* (mm)	23.48±0.54 (22.39 to 25.18)	23.45±0.70 (22.15 to 25.35)	P=0.60
Age* (years)	8.25±0.28 (7.69 to 8.75)	8.27±0.31 (7.75 to 8.75)	P=0.41
Gender (male %)	48.90%	55.17%	P=0.20
High myopia of parents	47.80%	55.17%	P=0.22

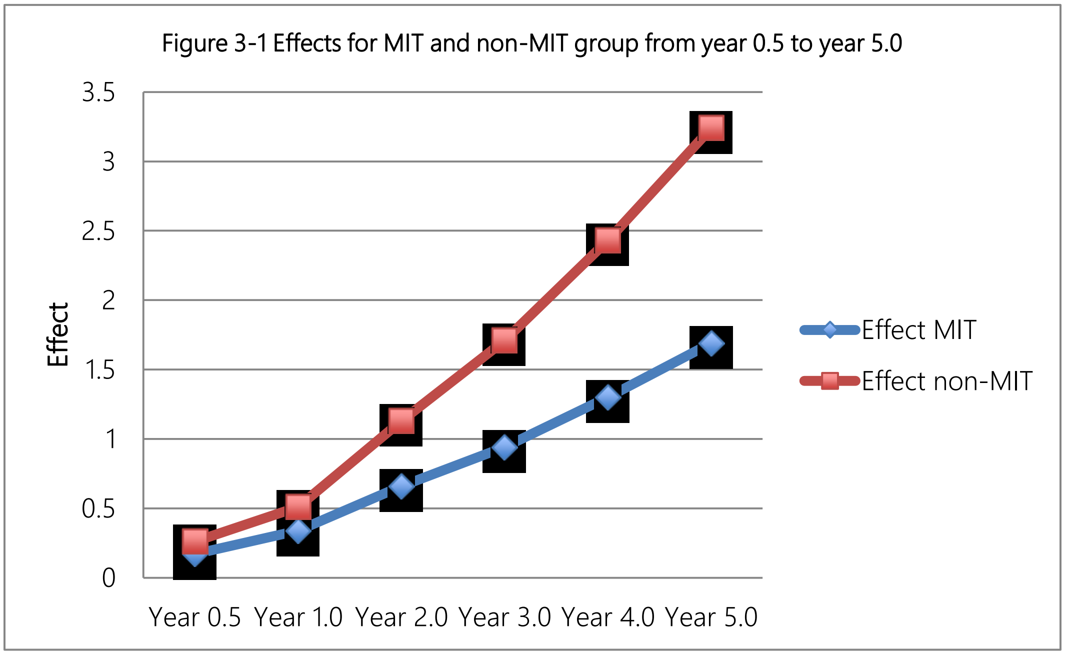
* mean±sd (min to max)

Given different treatments and interventions, the effects of myopia progression expressed as the increments of spherical equivalents revealed statistical differences shown in Table 3-2 and Figure 3-1.

Table 3-2 Summary statistics of effects (spherical equivalent increments) at different time points

Time of follow-up (year)	MIT (n=364), dse	non-MIT (n=174), dse	p-value
At recruitment (Year 0)	-0.81±0.43	-0.87±0.58	P=0.1381
Year 0.5*	0.17±0.21	0.26±0.25	P=0.0000
Year 1*	0.34±0.32	0.51±0.39	P=0.0000
Year 2*	0.66±0.52	1.13±0.69	P=0.0000
Year 3*	0.94±0.70	1.71±0.82	P=0.0000
Year 4*	1.30±0.90	2.43±0.98	P=0.0000
Year 5*	1.69±1.06	3.24±1.08	P=0.0000

* mean±sd, dse: spherical equivalent increment (myopia progression), p-value < 0.05 for statistical significance



The details of total costs for schoolchildren in MIT and non-MIT groups were listed in Table 3-3a. Health givers would get reimbursements as NTD 400 (USD 13.31) from the Taipei City Health Bureau or NTD 457 (USD 15.21) from the Health Promotion Administration, Ministry of Health and Welfare respectively. Co-payment was zero when schoolchildren presented the “Vision Protection Passport” to health providers at follow-up visits, or they had to pay co-payment NTD 200 (USD 6.66). Extra costs included schoolchildren school fee loss, the care’s wage loss and transportation cost; the amounts were approximate NTD 150 to 280 (USD 4.99 to 9.32) and NTD 150 to 350 (USD 4.99 to 11.65) for MIT and non-MIT groups respectively.

Table 3-3a Total costs details per case in MIT and non-MIT groups

Cost (NTD)	MIT (n= 364)	non-MIT (n= 174)	p-value
Atropine	21x (6 bottles/year)	21x (≤ 2 bottles/year)	
Health Insurance payment	400 (from Taipei City Health Bureau)	457 (from the National Insurance)	
co-payment	0.00	200.00	
Annual discount rate	3%	3%	
School fees lost	variable, some children using Saturday visit	variable, some children using Saturday visit	
Care's wage lost	variable (housewife, secretary, nanny, engineer, blue-collar)	variable (housewife, secretary, nanny, engineer, CEO, white-collar)	
Transportation cost	variable (bus, MRT, bike)	variable (bus, MRT, private driver)	
Mean total cost (sd)	8604.63(334.45)	8210.64(591.37)	0.0000

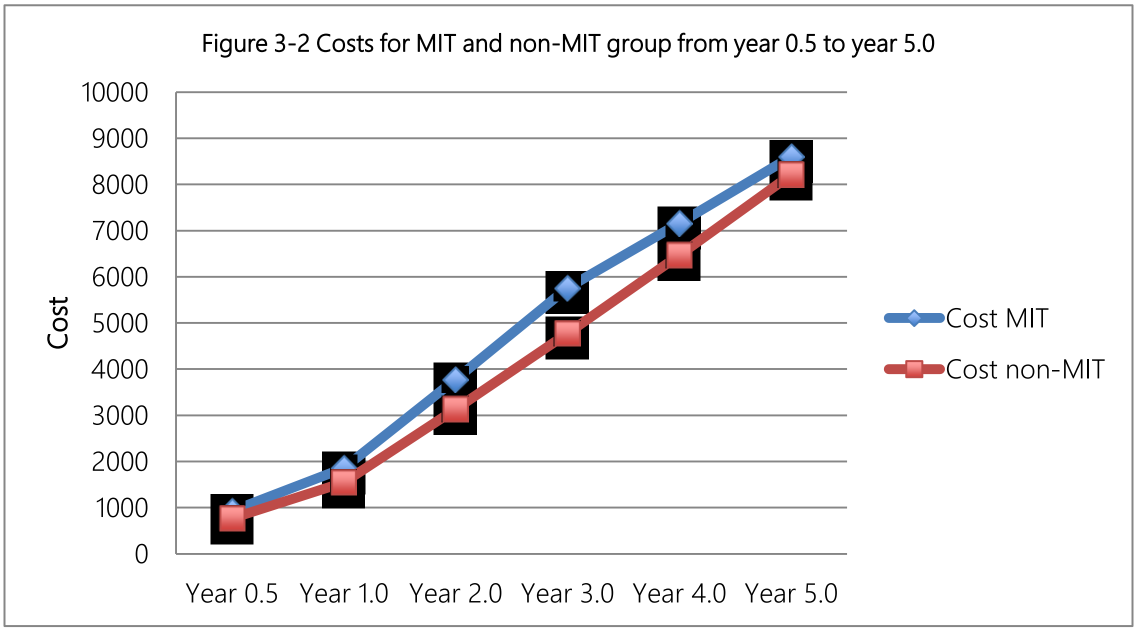
Children in MIT group got 2 free visits yearly for 3 years, then 1 free visit plus 1 regular visit with copayments per year for another 2 years. Extra costs were estimated around 150 to 280 according to travel distance.
MIT= (((400+457+0)+150)*2)*(POWER (0.97,4)+POWER (0.97,3)+POWER (0.97,2))+((400+457+200)+150*2)*(POWER (0.97,1)+1)
Children in non-MIT group received regular follow-up visit with co-payments per year for total 5 years. Extra costs were estimated around 150 to 350 according to travel distance and private driver usage.
non-MIT= (457+200+150)*2*(POWER(0.97,4)+POWER(0.97,3)+POWER(0.97,2)+POWER(0.97,1)+1)
1 USD = 30.042 NTD, 5/15/2018; annual discount rate = 3 %

The accumulated costs for each student from 0.5 year at the initiation of treatment till the last follow-up visit 5 years later were listed in Table 3-3b and Figure 3-2, all cost were statistically significant between MIT and non-MIT group. The costs between MIT and non-MIT group differed most at year 3.0 and approached together afterwards till year 5.0.

Table 3-3b Accumulated costs per case in MIT and non-MIT groups from year 0.5 to year 5.0

Cost (NTD)	MIT (n = 364)	non-MIT (n = 174)	p-value
Year 0.5	930.14(31.48)	771.98(55.47)	0.0000
Year 1.0	1861.05(62.88)	1543.65(111.18)	0.0000
Year 2.0	3779.66(127.70)	3135.03(225.80)	0.0000
Year 3.0	5757.61(194.53)	4775.64(343.97)	0.0000
Year 4.0	7159.44(263.42)	6466.98(465.79)	0.0000
Year 5.0	8604.63(334.45)	8210.64(591.37)	0.0000

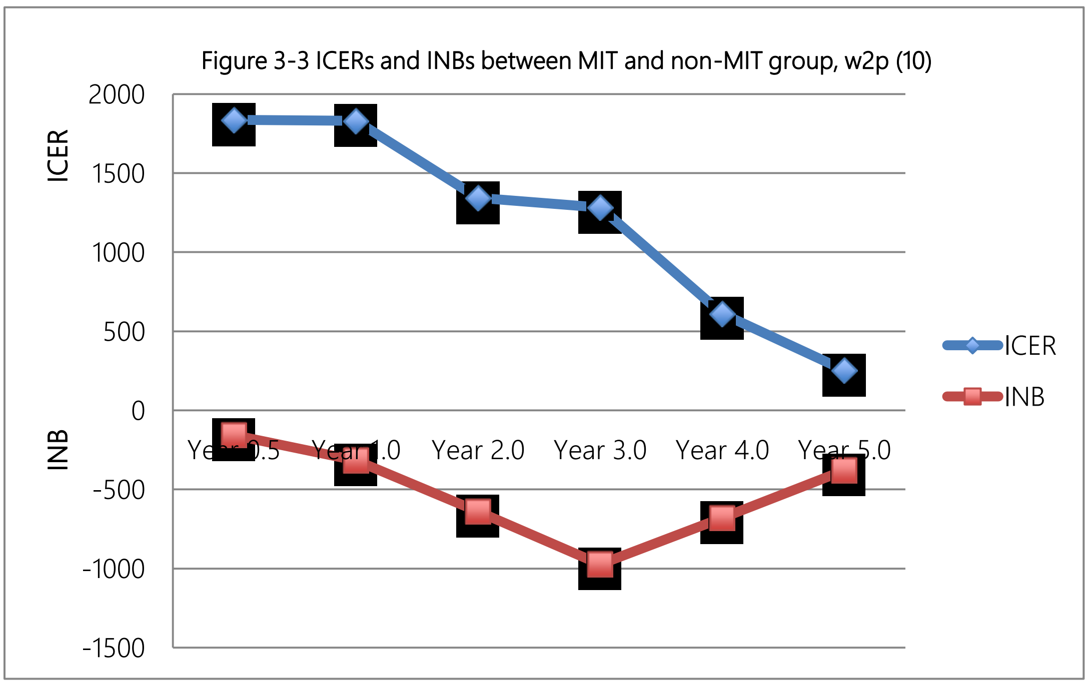
Mean(SD), p<0.05 for statistical significance
1 USD = 30.042 NTD, 5/15/2018; annual discount rate = 3 %



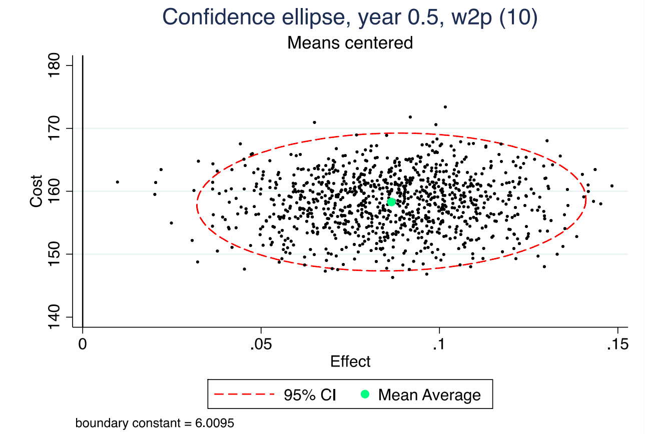
All ICERs and INBs were calculated between MIT and non-MIT group and listed in Table 3-4 and Figure 3-3 where $ICER_{year\ 0.5}$ and $INB_{year\ 0.5}$ were used as bases for comparison. Year 3.0 revealed as a turning point in Figure 3-1, where ICER had a big gap of 670.476(1282.426-611.951) and difference of INB was the highest (-817.013).

Table 3-4 Comparisons of ICERs and INBs from year 0.5 to year 5.0

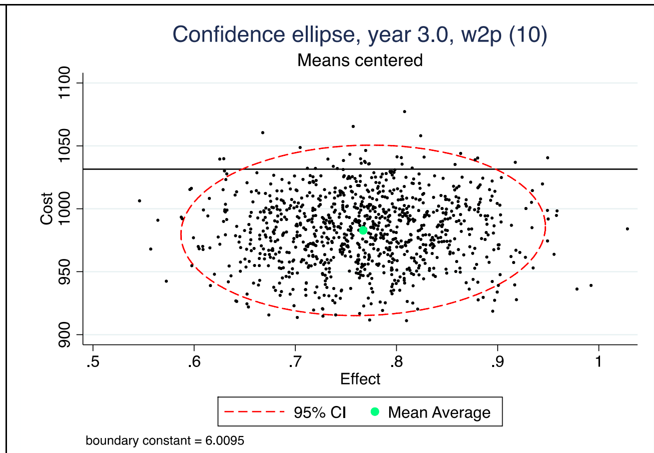
	ICER	INB	INB SE	CCC	Diff INB
Year 0.5	1837.305	-157.300	4.519	-	-
Year 1.0	1830.469	-315.672	9.022	0.357	-158.371
Year 2.0	1344.325	-639.832	18.329	0.108	-482.532
Year 3.0	1282.426	-974.313	27.974	0.061	-817.013
Year 4.0	611.951	-681.140	37.908	0.121	-523.840
Year 5.0	253.602	-378.452	48.133	0.168	-221.152



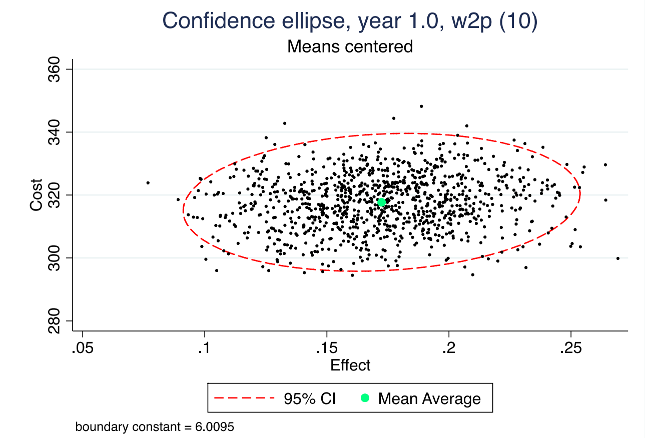
Bootstrap and Heapbs module analyses were used to produce confidence ellipse for different time points. For w2p (10), willing-to pay at NTD 10, as shown in Figure 3-4a to Figure 3-4f, probability of miscoverage = 100%, and probability of effectiveness = 0% for all time points.



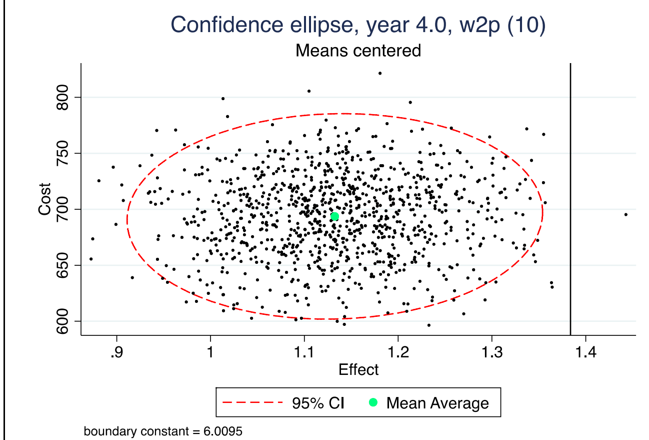
Probability of Miscoverage = 100%
Probability of Cost Effectiveness = 0%
Figure 3-4a Confidence ellipse at year 0.5, w2p (10)



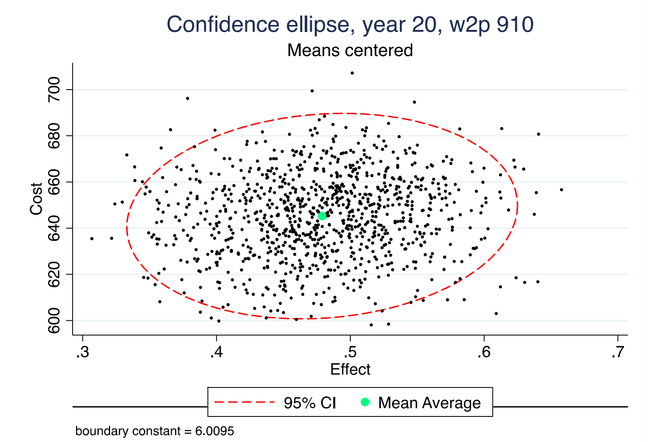
Probability of Miscoverage = 100%
Probability of Cost Effectiveness = 0%
Figure 3-4d Confidence ellipse at year 3.0, w2p (10)



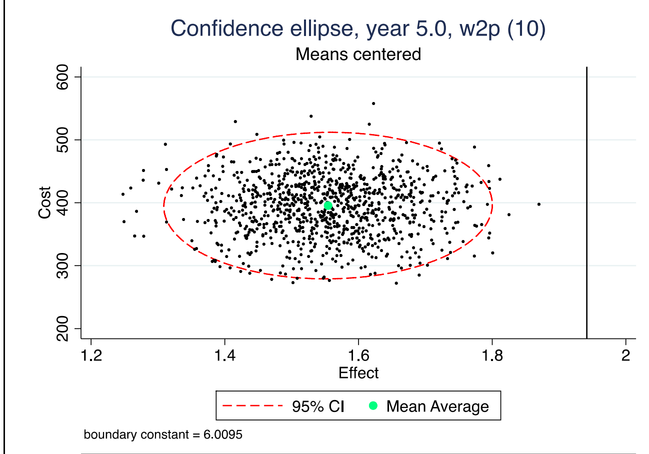
Probability of Miscoverage = 100%
Probability of Cost Effectiveness = 0%
Figure 3-4b Confidence ellipse at year 1.0, w2p (10)



Probability of Miscoverage = 100%
Probability of Cost Effectiveness = 0%
Figure 3-4e Confidence ellipse at year 4.0, w2p (10)



Probability of Miscoverage = 100%
Probability of Cost Effectiveness = 0%
Figure 3-4c Confidence ellipse at year 2.0, w2p (10)



Probability of Miscoverage = 100%
Probability of Cost Effectiveness = 0%
Figure 3-4f Confidence ellipse at year 5.0, w2p (10)

Figure 3-4a to 3-4f Confidence ellipses from year 0.5 to year 5.0, w2p (10)

INB300 (Incremental Net Benefit, w2p (300)) > 0 at year 5.0, INB1000 (Incremental Net Benefit, w2p (1000)) > 0 at year 4.0 and year 5.0 are revealed in Table 3-5 and Figure 3-5.

Table 3-5 Comparisons of ICERs and INBs for w2p (10, 300, 1000) from year 0.5 to year 5.0

Year	ICER	INB10	INB300	INB1000
Year 0.5	1837.305	-157.300	-132.336	-72.078
Year 1.0	1830.469	-315.672	-265.385	-144.004
Year 2.0	1344.325	-639.832	-500.772	-165.110
Year 3.0	1282.426	-974.313	-752.256	-216.257
Year 4.0	611.951	-681.140	-352.989	439.099
Year 5.0	253.602	-378.452	72.082	1159.578

ICER: Incremental Cost Effectiveness Ratio
INB10: Incremental Net Benefit, w2p (10)
INB300: Incremental Net Benefit, w2p (300)
INB1000: Incremental Net Benefit, w2p (1000)

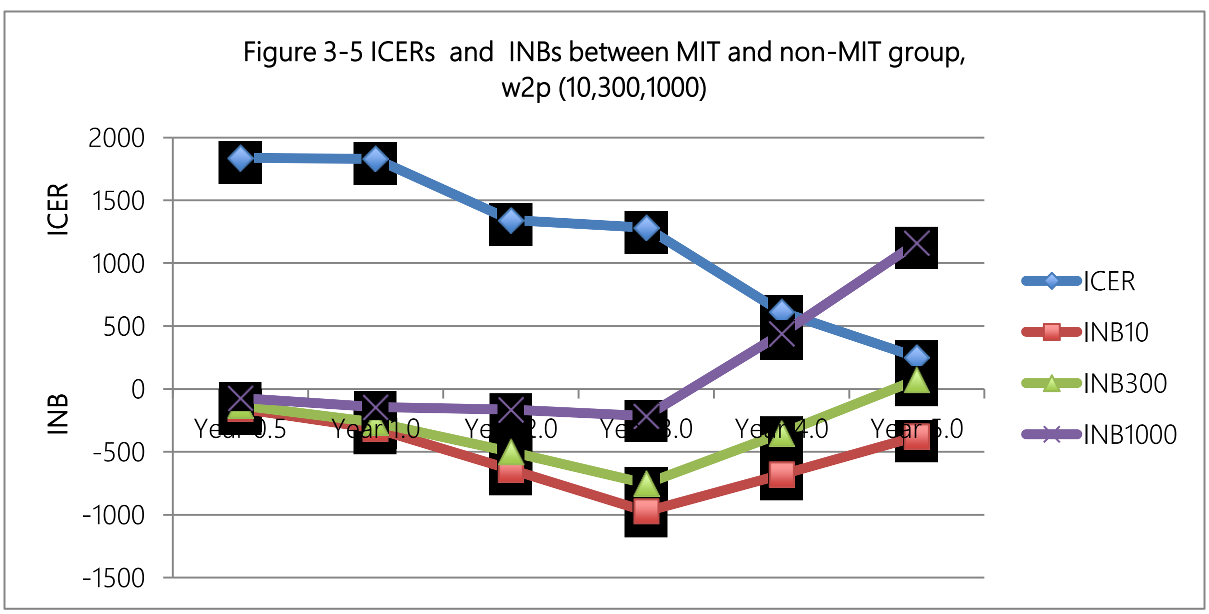


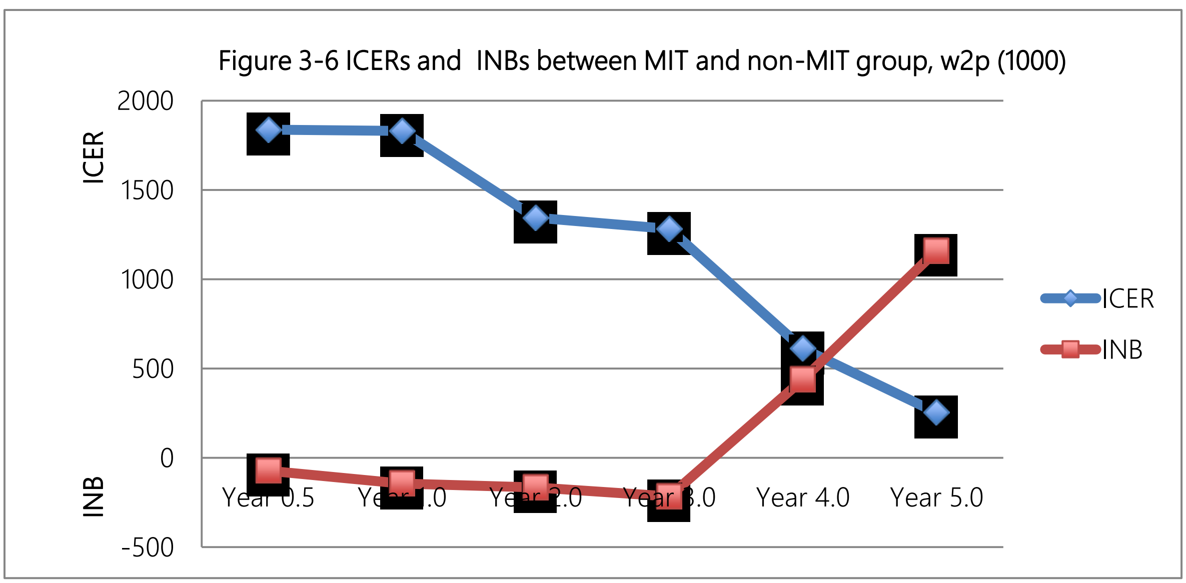
Figure 3-5 ICERs and INBs between MIT and non-MIT group, w2p (10,300,1000)

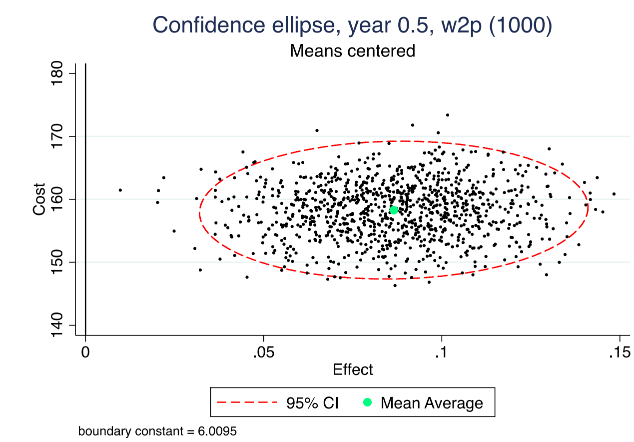
For w2p (1000), willing-to pay at NTD 1000, INB (Incremental Net Benefit) turns to be positive as shown in Table 3-6 and Figure 3-6; probability of miscoverage = 100%, and probability of effectiveness = 100% for year 4.0 and year 5.0 as shown in Figure 3-6e and Figure 3-6f.

Table 3-6 Comparisons of ICERs and INBs from year 0.5 to year 5, w2p (1000)

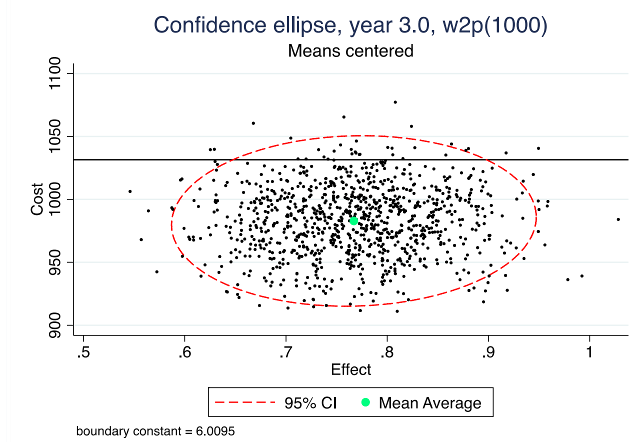
Year	ICER	95% CI of ICER	INB	INB SE	CCC	Diff INB
Year 0.5	1837.305	211.0814 - 3463.529	-72.078	22.162	-	-
Year 1.0	1830.469	1041.683 - 2619.256	-144.004	34.207	0.671	-71.927
Year 2.0	1344.325	994.7090 - 1693.940	-165.110	59.741	0.400	-93.032
Year 3.0	1282.426	1027.738 - 1537.114	-216.257	76.321	0.291	-144.179
Year 4.0	611.951	496.3881 - 727.5134	439.099	95.188	0.193	511.177
Year 5.0	253.602	185.3872 - 321.8169	1159.578	109.371	0.112	1231.656

ICER: Incremental Cost Effectiveness Ratio
INB: Incremental Net Benefit, Diff INB: Difference between INBs
CCC: Lin's concordance correlation coefficient

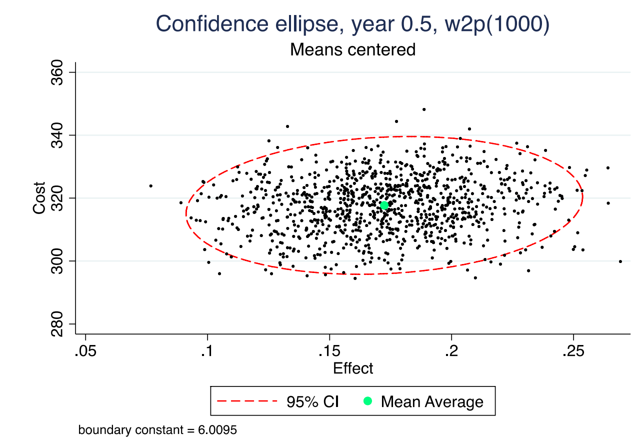




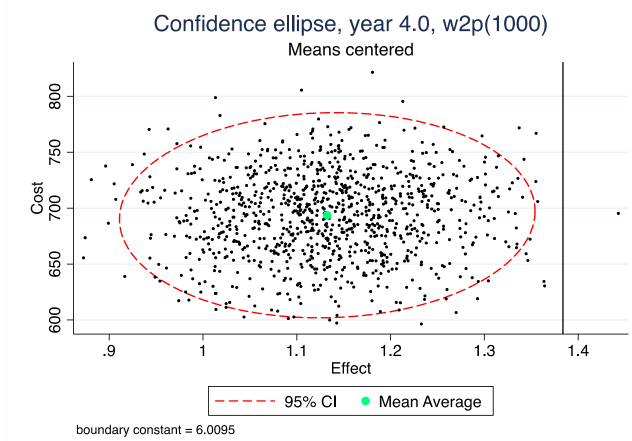
Probability of Miscoverage = 58.1%
Probability of Cost Effectiveness = 0%
Figure 3-6a Confidence ellipse at year 0.5, w2p (1000)



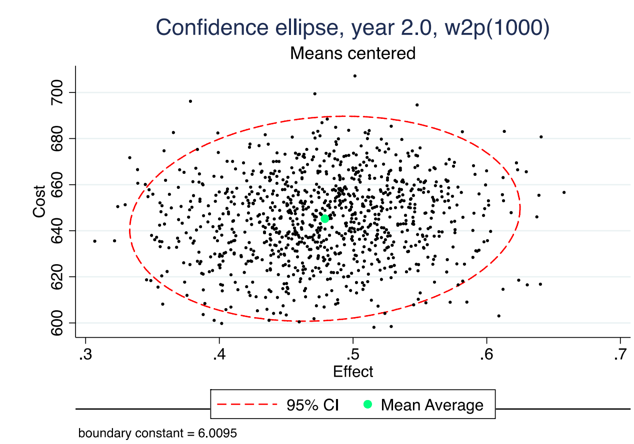
Probability of Miscoverage = 100%
Probability of Cost Effectiveness = 0.3%
Figure 3-6d Confidence ellipse at year 3.0, w2p (1000)



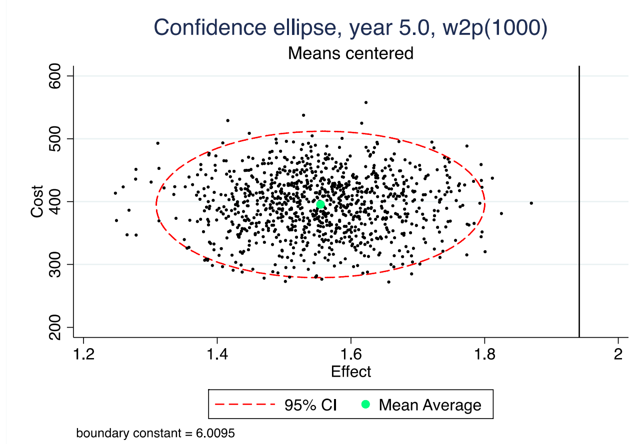
Probability of Miscoverage = 90.7%
Probability of Cost Effectiveness = 0%
Figure 3-6b Confidence ellipse at year 1.0, w2p (1000)



Probability of Miscoverage = 100%
Probability of Cost Effectiveness = 100%
Figure 3-6e Confidence ellipse at year 4.0, w2p (1000)



Probability of Miscoverage = 98.8%
Probability of Cost Effectiveness = 0.5%
Fig 3-6c Confidence ellipse at year 2.0, w2p (1000)



Probability of Miscoverage = 100%
Probability of Cost Effectiveness = 100%
Figure 3-6f Confidence ellipse at year 5.0, w2p (1000)

Fig. 3-6a to 3-6f Confidence ellipses from year 0.5 to year 5.0, w2p (1000)

Discussion

The myopia prevalence of primary schoolchildren in Taiwan, less than Singapore, was ranked as the second highest in the world (Liou, 2019). In a study of 928 schoolchildren in Singapore, Chua reported that children getting myopia at their younger ages or having longer duration of myopia progression were more likely to develop high myopia (odds ratio = 2.86) in their later life. (Chua et al., 2016) Thus controlling early onset of myopia to delay its progression will lead to reduce the risk of morbidity associated with high myopia. (Tran et al., 2018)Thus we said “The younger the myopes, the older the high-myopes.” to emphasize the importance of early treatment of myopia to the parents. Compared to orthokeratology (OK) lenses, atropine eye drops remain the most popular treatment to delay myopia progression in Taiwan because of its easiness for use and minimal co-payment or out-of pocket expenditure; however, there were several different concentrations of atropine to choose. The principles behind seasonal modification of atropine use were preserving efficacy and minimizing complication, (Lu, P. C. & Chen, 2010)and we found the combined regimen of three concentrated atropine eye drops were both more effective and less expensive than one concentration alone.

Zheng analyzed the economic cost of 113 Singaporean adults aged 40 years and older with myopia at least -0.5 diopters and found that myopia was not only a considerable economic burden for patients but also a disorder with tremendous societal costs, approximate USD 755 million per year, and a huge public health impact. (Zheng et al., 2013) MIT program gives the parents motives for continuation to seek effective treatment to delay myopia progression with the nightmare of high myopia by providing financial supports and reliable ophthalmologists in Taipei City. Schoolchildren from non-MIT group are lack of consistency of atropine treatment without reminder from MIT program or schoolteacher.

Out-of-pocket expenditure is minor issue because of some schoolchildren coming from areas within walking distance to clinic, the convenience of public transportation (bus, MRT, U-bike) in Taipei City and some free parking space provided by clinic for parents or private driver. The mean costs shown in Figure 3-2 are higher in MIT than non-MIT group, climbing up from year 0.5 (ΔNTD 158.16 = ΔUSD 5.26), year 1.0 (ΔNTD 317.41 = ΔUSD 10.57), year 2.0 (ΔNTD 644.63 = ΔUSD 21.46), and to the top at year 3.0 with the most disparity (ΔNTD 981.97 = ΔUSD 32.69), then sliding down to year 4.0 (ΔNTD 692.46 = ΔUSD 23.05) and to the second lowest at year 5.0 (ΔNTD 393.999 = ΔUSD 13.11). Those are the trends of incremental costs between MIT and non-MIT group. The effects for MIT and non-MIT group are defined as the increments (or difference) of myopia equivalent (dse) between the initiation of treatment (year 0) and the following time point (year t). The mean effect gaps (Δdse) between MIT and non-MIT shown in Figure 3-1 getting larger indicates the effects of myopia control are more evident at year 5.0 (Δdse = 3.24-1.69 = 1.55D) than year 0.5 (Δdse = 0.26-0.17 = 0.09D). The more myopia progression the worse outcome, thus myopia has detrimental effect and MIT group revealed a better outcome than non-MIT group (1.69D vs. 3.24D) at year 5.0.

In this dataset, we compare ICERs and INBs for w2p (10), willing-to-pay at NTD 10, in Table 3-4 and Figure 3-3 and find that ICERs keep the same level (1837.305 vs. 1830.469) while worse INBs (-1.57.300 vs. -315.672) for year 0.5 and year 1.0. That implies the cost-effectiveness is not comparable with the net benefit between MIT and non-MIT group within the first year follow-up. From year 1.0 to year 3.0, ICER and INB appear parallel trend. The turning point of INBs accompanying with a sharp slope of ICER trend at year 3.0 indicates that myopia progression slowing down further afterwards till the end of follow-up at year 5.0. However the confidence ellipses of bootstrapping with replications 1000, reps (1000), for year 0.5 to year 5.0 shown in Figure 3-4a to 3-4f all revealed the results of " Probability of Miscoverage = 100% and Probability of Cost Effectiveness = 0". Those results might be due to willing-to-pay (w2p) not high enough.

The results in Table 3-5 and Figure 3-5 suggest that if willing-to-pay (w2p) increases from NTD 10 to NTD 300, the Incremental Net Benefit (INB) for year 5.0 will turn to be positive (72.082). The average costs for each visit listed in Table 3-3b for MIT and non-MIT group are 930.14 and 771.98 respectively. ICERs keep the same trend whatever willing-to-pay varies fro 10 to 300 or even to 1000; however, INBs for w2p (1000), willing-to-pay at NTD 1000, while after the turning-point at year 3.0, Incremental Net Benefit (INB) becomes positive value of 433.099 at year 4.0 and climbs up to value of 1155.578 at year 5.0.

The confidence ellipses of bootstrapping with replications 1000 for year 4.0 and year 5.0 shown in Figure 3-6e and Figure 3-6f both revealed the results of " Probability of Miscoverage = 100% and Probability of Cost Effectiveness = 100%". These results indicate that compared to non-MIT group, the modified atropine use in MIT group reveal cost-effective after following-ups at least 4 years as long as willing-to-pay equal to or higher than NTD 1,000.

The results of ICER, between MIT and non-MIT group, dropping from 1837.305 at year 0.5 dramatically to 253.602 at year 5.0 are implicated that for delaying myopia progression, the costs will decrease more and more for long-term atropine eye drops use modified with seasonal change and the severity of myopia. And INB under w2p (1000) turned from -72.078 at year 0.5 to 1159.578 at year 5.0 suggest a desirable investment for the government, not only to prevent ocular deterioration from high myopia but also to reduce cost of healthcare. Further researches should aim to develop and provide more solid and longitudinal data to generalize the economic model.

There is no previous cost-effectiveness study ever been conducted on the combination therapy of modified atropine eye drops in a High-tech Science Park with high income setting to allow comparison of results.

Study Limitations

Cost of the MIT education intervention components: (1) ”Vision Protection Passport”, (2) School teacher and nurse’s efforts to reduce eating garbage foods and keep healthy day-to-day lifestyle. NTD 400 is underestimated though. Costs of public school lunch are fixed and regulated by education bureau. But it is varied a lot in private school. So it is hard to compare.

The time costs were not recorded since the time spent with the child by the ophthalmologist and optometrist was assumed to be the same for all MIT and non-MIT group. The extra costs were estimated by simple interviews with parents. Side effects for long-term atropine user, especially photophobia and difficulty in near-works, and the duration of side effects were not assessed, even side effects tended to be mild and easily to be overcome by sunglasses or progressive glasses. This study is confined with small sample size with special data setting, and relative costs and effectiveness of atropine therapy may vary between populations, and therefore more studies are needed before assessing whether the results are generalizable to other populations; even we do not use expensive equipment or eye drops and try to make our study results reflecting the real-world circumstances in Taiwan.

Study strength and Public Health Implications

This prospective and longitudinal study confirms that combination of 0.125%, 0.25% and 0.5% atropine as well as daily life interventions such as “853240” in MIT group are more effective than irregular therapy regimen. All schoolchildren completed the follow-ups every six months without major side effects reported.

Economic evaluations can provide “value-for- money” information to those decision- makers about the allocation of limited health care resources and can be used to identify the worthy interventions for treatments and therapies. (Mitton, Dionne, & Donaldson, 2014) We thus propose MIT program should be expanded to other urban and rural schools and extended to kindergarten and junior high schools for more effective control of myopia progression as soon as possible.

Chapter 4

Assessment of the Taiwan Visual Function Questionnaire (Twn VFQ-25) for Primary School Students: Are Near Vision and Distance Vision Affected under Atropine Control for Myopia Progression

Abstract

Purpose

To validate Taiwan Visual Function Questionnaire (Twn VFQ-25) and to asses the quality of life in schoolchildren of primary school as well as to evaluate the impacts on near vision and distance vision for those using atropine eye drops.

Design

A prospective observational study with interviewer-administered survey questionnaire.

Participants

The children of primary school having joined MIT (Myopia Intervention Study in Taipei city) program and continuing atropine eye drops use for at least six months were recruited. Students from non-MIT group served as controls. Students with spherical equivalent at least -0.25 diopters (D), astigmatism power no more than 2.0 D and corrected vision as 1.0 (20/20) were eligible for this study. Students with previous ocular trauma, amblyopia, cataract, keratoconus, myopia over -10.0 D, ocular hypertension, glaucoma or OK (orthokeratology) lens wearers were excluded. Questionnaire data were available for 247 participants consisting of 125 students from MIT group (n = 125) and 122 students from non-MIT group (n = 122).

Methods

For MIT group, combined with the interventions of “853240” as guidance for healthy lifestyle, 0.10% atropine eye drops were used in summers, 0.25% used in springs and falls, and 0.50% used in winters according to seasonal sunlight intensity and the severity of myopia. All recruited schoolchildren completed the 25-item Taiwan Visual Function Questionnaire (Twn VFQ-25). Cronbach's alphas were evaluated with multivariate analysis. The original responses of questionnaire were transformed to scores and the scores of questionnaire subscales were compared between MIT and non-MIT group using student t-test. Ordered logistic regression model (UCLA, 01072020) was used to evaluate the impacts on near vision and distance vision for atropine users. Stata/IC 15.1 was applied for statistical analysis.

Main Outcome Measures

Twn VFQ-25 scores.

Results

Two hundred and forty seven participants, comprising one hundred and twenty five schoolchildren from MIT group (n = 125) and non-MIT group (n = 122) completed the Twn VFQ-25. Mean ages were 9.72±1.54 years (range from 6.88 to 12.70 years) and 9.56±1.29 years (range from 6.95 to 12.02 years) for MIT and non –MIT groups respectively. There were 52.80% and 49.18% boys in MIT and non –MIT groups respectively. All Cronbach's alpha coefficients values of reliability tests were higher than 0.70, except in Part I General health, for Taiwan Visual Function Questionnaire (Twn VFQ-25) to evaluate the vision related quality of life for schoolchildren in primary schools. All scores of 11 subscales were not statistically significant at the 0.05 level between MIT and non-MIT group. For MIT group, the odds of being in a higher level of Q61 (watching blackboards) are 1.25 (95% CI (0.65 - 2.41), p = 0.506) times greater than for non-MIT group, given the other variables are held constant in the model. For a one unit increase in Q5 (reading textbook), the odds of being in a higher level of Q61 (watching blackboards) are 1.03 (95% CI (1.01 - 1.05), p = 0.001) times greater given the other variables are held constant in the model. Holding the other variables at a fixed value, a one year increase in age would result in a 0.71

(95% CI (0.55 - 0.91), p = 0.006) times lower of the odds of being in a higher level of Q61 (watching blackboards). Holding the other variables at a fixed value, for males (gender = 1), the odds of being in a higher level of Q61 (watching blackboards) are 0.61 (95% CI (0.31 - 1.20), p = 0.154) times lower than for females (gender = 0). The preference scores of “853240” in MIT group were ranked as follows: 75.04(8)> 56.96(4)> 54.40(2)> 42.88(5)> 38.72(0)> 32.00(3). “Sleeping well for at least 8 hours (8)” was most preferred by schoolchildren in MIT group and had a positive correlation with “eating 5-kind of colorful vegetables and fruits daily (5)”.

Conclusions

The Taiwan Visual Function Questionnaire (Twn VFQ-25) was validated for evaluating the vision related quality of life for schoolchildren in primary schools. Near vision and distance vision were not affected by atropine use. A one unit increase in Q5 (reading textbook), the odds of being in a higher level of Q61 (watching blackboards) are 1.03 (95% CI (1.01 - 1.05), p = 0.001) times greater given the other variables are held constant in the model.

Introduction

The importance of myopia

Myopia, or nearsightedness, remains the most common vision disorder and leading cause of visual impairment over the whole world; however, even there is no really safe level of myopia, it has been overlooked most of time (Miraldi Utz, 2016; NIH, 2010). Myopic eye globe is larger than normal (Matsumura et al., 2019) and becomes even larger and pointed in pathological myopia eye to an extreme extent thus results in retinal tears, holes, and even detachment in the retina (NIH, 2010). Myopia is classified into three degrees as low myopia (less than 3.00 D), medium myopia (3.00 to 6.00 D), and high myopia (greater than 6.00 D). Development of myopia could be divided into four stages of life: (1) congenital myopia is diagnosed at birth and persists through infancy, (2) youth-onset occurs in children less than 20 years of age, (3) early adult-onset of myopia occurs in individuals less than 40 years of age and (4) late adult-onset of myopia is diagnosed among those older than 40 years of age (Goss et al., 2006) There are 153 million individuals worldwide, estimated by the World Health Organization (WHO), visual impairment due to uncorrected refractive error (Kuang et al., 2016). Holden estimated that 1.4 billion persons or 22.9% of the world population are myopic, and 163 million persons or 2.7% of the world population are high myopic in year 2000 (Holden, B. A. et al., 2016). Growing prevalence and associated severe comorbidities of myopia make it a concerning vision disorder. High myopia is associated with retinal degeneration, glaucoma, cataract, visual impairment and even blindness (Huang et al., 2015). Incidence of myopia is rising and the prevalence of myopia in the US has increased from 25% to 44% in the last 30 years (Miraldi Utz, 2016)In Asian countries, the prevalence of Myopia can be as high as 80% among young adult populations (Miraldi Utz, 2016). By year 2020, the prevalence of myopia is expected to be about 2.5 billion persons (Miraldi Utz, 2016). By year 2050, there is going to be 4.95 billion or 52.0% of the world population with myopia as shown in Figure 1-1, Chapter 1 and almost 0.925 billion people or 10.0% of the world population with high myopia as shown in Figure 1-2, Chapter 1 (Holden, B. A. et al., 2016). Urbanization and increased academic pressures contribute to the rising prevalence of myopia (Huang et al., 2015). One of the leading environmental risk factors for myopia is near work, which is defined as activities done at short distance from the eye such as reading, studying, writing, using computers, playing video games, and watching TV (Huang et al., 2015). The inclusion of phones, tablets, and other electronic devices as a risk factor for myopia does not yet have sufficient evidence to support an association; with a few studies assessing their impact, in addition to screen size, text size, and other factors (Lu, B. et al., 2009). Studies have shown that myopic children spend more time on reading compared to non-myopic children, with no significant differences in studying, using a computer, or watching TV (Huang et al., 2015). Thus, reading is hypothesized to be the main near work activity associated with myopia (Huang et al., 2015). The term “school myopia” was coined, referring to myopia that tends to develop among school-aged children, perhaps as a result of near work behaviors (Huang et al., 2015; Miraldi Utz, 2016).

“School myopia” is the most common type of non-pathologic myopia diagnosed among schoolchildren (Miraldi Utz, 2016). Myopia usually develops around the age of six to eight years and progresses through the age of 15 or 16 years at rate of 0.50 diopters (D) per year in Western children and 1.00 D in Asian children (Huang et al., 2015; Lu, P. C. & Chen, 2010). Other studies have confirmed that myopia can progress twice as fast among Asian children compared to Western children (Huang et al., 2015). This can be explained by differences in educational systems, pressure on academic performance, and influence on spending more time on near works in eastern countries compared to a focus on physical education and spending more time on sports and outdoor activities in western countries (Huang et al., 2015). Spending extra hours after school on near works is hypothesized to worsen progression of myopia among Asian children (Huang et al., 2015; Mutti et al., 2002; Saw et al., 2000; Saxena et al., 2015).

Simple myopia in children and adults are the most common among various types of myopia reported by Goss. Other types include nocturnal myopia, pseudomyopia, degenerative myopia, and induced myopia. Nocturnal myopia refers to difficulty seeing at night or in dimly light areas. Pseudomyopia results from increased ocular refractive power due to overstimulation of the eye. Degenerative myopia, also known as pathological myopia, is a high degree of myopia with severe degenerations over the posterior pole of the eye. Induced myopia is often short-term and may be reversible, which is acquired from exposure to certain pharmaceutical products, changes in blood sugar levels, nuclear sclerosis of the crystalline lens, or other causes (Goss et al., 2006).

In addition to economic and psychosocial implications, myopia also increases the risk for comorbidities such as myopic macular choroidoretinal degeneration and neovascularization, myopic retinoschisis and even retinal detachment and decreases quality of life (Bourke et al., 2019; Miraldi Utz, 2016). Study has shown that participants over the age of 54 with levels of myopia ranging from -6 to -10 diopters (D) had an odds ratio of 3.4 as a lifetime risk for visual impairment; the odds ratio was 22 for those with myopia levels greater than -10 D (Miraldi Utz, 2016). To address these concerns, the Vision 2020 initiative by WHO listed myopia as one of the top five immediate priorities (Huang et al., 2015).

Risk Factors of Myopia

Genetic and environmental risk factors both contribute to myopia. Studies have shown that myopia progresses faster when it develops at a young age, and that early-onset myopia is associated with high myopia later in life (Wu et al., 2013). A major risk factor for progression of myopia among older children and adolescents is axial elongation of the posterior segment (Lee, M. W. et al., 2019; Lu, P. C. & Chen, 2010; Matsumura et al., 2019; Miraldi Utz, 2016). Changes in the axial length and refractive power of the eye leading to emmetropia or low-grade hypermetropia are caused by emmetropization, which involves a complicated array of vision-driven retinal signaling (Miraldi Utz, 2016). Myopic eyes presenting longer axial lengths are demonstrated by Matsumura with MRI and AI techniques (Matsumura et al., 2019). It is hypostasized that caused by signaling cascades in the retina followed by a choroidal response and scleral matrix remodeling (Miraldi Utz, 2016). Experimental studies have induced myopia in animal subjects by altering the visual experience-driven signaling cascades through placing a minus lens during early development, causing hypermetropic defocus and myopic progression (Miraldi Utz, 2016). Other risk factors include patient age, intraocular pressure, refractive powers of the cornea, lens, axial length, and aqueous and vitreous refractive indices, all of which contribute to the refractive state of the eye (Han, X. et al., 2018; Miraldi Utz, 2016). Genetic factors, such as susceptibility variants within any gene encoding (Miraldi Utz, 2017)proteins in these signaling cascades, can contribute to a myopic phenotype (Miraldi Utz, 2016; Miraldi Utz, 2017; Stokman et al., 2016; Storm et al., 2014). Myopia is categorized as either syndromic or non-syndromic (Cai et al., 2019; Flitcroft et al., 2018; Miraldi Utz, 2016; Tedja et al., 2019; Vishweswaraiah et al., 2019). Syndromic myopia is defined as systemically inherited disease that tends to be inherited in a Mendelian fashion (Flitcroft et al., 2018; Miraldi Utz, 2017; Tedja et al., 2019). Non-syndromic myopia refers to myopia present in a group of patients with a strong familial clustering of the trait but without other systemic traits (Miraldi Utz, 2016; Vishweswaraiah et al., 2019). A drastic rise in the prevalence of “school myopia” in different regions of the world supports an environmental cause (Miraldi Utz, 2016; Yotsukura et al., 2019) As the nature vs. nurture debate continues, there are more evidences revealing the gene-environment interactions at play in myopia progression. For example, children of myopia parents tend to spend more time in environments that increase the risk of myopia (Miraldi Utz, 2017; Morgan & Rose, 2019). It has also shown that having a risk allele change retinal image and contrast processing can lead to myopia in those who read intensely (Enthoven et al., 2019; Pozarickij et al., 2019; Tang et al., 2019).

Many studies have shown that outdoor play with exposure to natural light is preventative against progression of myopia (Cao, K. et al., 2019; Guggenheim et al., 2012; Miraldi Utz, 2016). Lower rates of myopia occur where environmental and behavioral risk factors are not present, such as rural areas where exposure to natural light is more common than in urban areas (Cao, K. et al., 2019; Miraldi Utz, 2016). Higher levels of education and near work are associated with development of myopia (Miraldi Utz, 2016). In summary, age, genes and parental refractive error, time spent outdoors and time spent doing near work are suspected risk factors for myopia. Causal and associative relationships between risk factors and myopia in the literature are still not consistent and more research is needed to better understand heritability, gene-environment interactions, and other risk factors.

Myopia in Taiwan

Taiwan was coined the “the island of myopia” and “myopia capital of the world” in 1999. (Chang, 1999) Table 1-A and Table 1-B, Chapter 1 revealed myopia and high myopia prevalence of schoolchildren from year 1986 to year 2018 (HPA, 2018). The myopia prevalence of the sixth grade (63.3%) was 2.39 folds higher than the first grade (26.5%) in year 2018 (HPA, 2018). The myopia prevalence of primary schoolchildren in Taiwan, less than Singapore, was the second highest in the world (Liou, 2019)

Enthoven in the “Generation R study” discussed the interaction between lifestyle and genetic susceptibility in myopia and concluded that putting a major focus in the prevention of myopia on adjustment of lifestyle due to the popularity of myopia genes in general people. (Enthoven et al., 2019) Myopia Intervention in Taipei (MIT) program is sponsored by Taipei City Health Bureau and offers a free myopic status ocular examination at contracted ophthalmic clinics or hospital for the primary schoolchildren once or twice a year, besides, there are so called “853240” behavior modalities input to their day-to-day life activities.

Quality of vision and life are very important for schoolchildren to learn happily without too much education pressure. Taiwan Visual Function Questionnaire-25 (Twn VFQ-25) is a modified NEI VFQ-25 (RAND, 2019), containing 25 vision-targeted questions within 11 vision-related subscales (Chan, Wong, Lam, McGhee, & Lai, 2009; J. C. Lin & Chie, 2010; Mollazadegan et al., 2014; Wang, Chan, & Jin, 2008), is used to compare the overall score of impacts on schoolchildren vision-related quality of life between MIT group and non-MIT control group. By identifying and reducing the risk factors during myopia treatment, patient's quality of life, health and safety, inconveniences in daily activities should be improved and thereby putting positive effects on their socio-economic impacts (Bourke et al., 2019; Kandel, Khadka, Goggin, & Pesudovs, 2017)

Methods

The schoolchildren in primary school having joined MIT (Myopia Intervention in Taipei city) program and continuing atropine use for at least 6 months were recruited. Students from non-MIT group served as controls. The inclusion criteria included: 1. spherical equivalent at least -0.25 diopters (D) for both eyes, 2. astigmatism power not higher than 2.0 D, and 3. the best corrected vision being 1.0 (20/20). The exclusion criteria included: 1. previous ocular trauma, 2. amblyopia, 3. early-onset cataract, 4. keratoconus, 5. myopia over -10.0 D, 6. ocular hypertension, 7. glaucoma, and 8. OK (orthokeratology) lens wearers. Total 247 participants consisting of 125 students from MIT group (n = 125) and 122 students from non-MIT group (n = 122) were interviewed to complete Taiwan Visual Function Questionnaire (Twn VFQ-25).

Three different concentrations of atropine eye drops were used, according to seasonal sunlight intensity and the severity of myopia, in MIT group. The general guidelines for atropine eye drops were 0.10% atropine eye drops used in summers, 0.25% in springs and falls, and 0.50% in winters. For those very low myopes (-0.75D to -0.25 D), the frequency of instillation was reduced to once or twice a week one month after initiation of treatment. Anti-ultraviolet sunglasses were prescribed for subjects who had outdoor activities and progressive spectacles were given for children who had difficulty in reading or writing. Not only atropine use, the multifactorial interventions were also applied in daily life for MIT group.

Taiwan Visual Function Questionnaire (Twn VFQ-25)

The modified bilingual version of Twn VFQ-25 was revealed at appendix, in which Question 6.1 regarding vision for watching blackboards at classroom was added to evaluate the distance vision, and Question 15, 15a, 15b and 15c regarding driving a car were replaced with riding a bicycle to fit the schoolchildren usual day-to-day life in primary school.

The original responses categories were transformed from 0 to 100 scores as shown in Table 4-C (RAND, 2019).

Table 4-C Scoring Key: Recording of Items

Item Numbers	Original response category	Recorded value
1,3,4,15c	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
5,6,6.1,7,8.9,10,11,12,13,14,16,16a	1	100
	2	75
	3	50
	4	25
	5	0
	6	*
17,17,19,20,21,22,23,24,25	1	0
	2	25
	3	50
	4	75
	5	100

(a) Precoded response choices as printed in the questionnaire.

(b) Item 15c has four-response levels, but is expanded to a five-levels using item15b.

Note: If 15b=l, then 15c should be recoded to "0"
If 15b=2, then 15c should be recoded to missing.
If 15b=3, then 15c should be recoded to missing.

* Response choice "6" indicates that the person does not perform the activity because of non-vision related problem. If this choice is selected, the item is coded as "missing."

The items to be averaged for generating subscales scores were listed in Table 4-D (RAND, 2019).

Table 4-D VFQ-25 Subscales and Items for Averaging

Subscales	Number of Items	Items to be averaged
General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	4	6.1, 8, 9, 14
Vision Specific:		
Social Functioning	2	11, 13
Mental Health	4	3, 21, 22, 25
Role Difficulties	2	17, 18
Dependency	3	20, 23, 24
Riding	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

The scores for preference of “853240”

The so called “853240” interventions were illustrated as follows: “8” for at least 8-hour sound sleep; “5” for daily consuming 5-kind of colorful vegetables and fruits; “3” for 3 ninety angles (ankle, knee and hip) while sitting with 2 flat planes (both arms resting flat on desk) and 1 line for ear, shoulder and hip; “2” for at least 2-hour outdoor activity every day; and “4” for 4 3Cs (TV, iPad, computer, smart phone) use at most one hour per day; “0” for 10–minute rest every 30-minute eye use.

The ranking of preference of “853240” is assigned from 1 (most preferred) to 6 (least preferred); and the scores shown in Table E were transformed as 100 for preference 1, 80 for preference 2, 60 for preference 3, 40 for preference 4, 20 for preference 5, and 0 for preference 6. All data were retrieved from Harvard Vision Center.

Table 4-E Scoring key for preference of "853240"

Original preference response	Recorded score
1	100
2	80
3	60
4	40
5	20
6	0

Statistical analysis

Cronbach's alpha was evaluated with multivariate analysis and the scores of questionnaire subscales were compared between MIT and non-MIT group using student t-test. Spearman’s rank correlation test was used to analyze the preference scores of “853240” interventions. Ordered logistic regression model (UCLA, 01072020) was used to evaluate the impacts on near vision and distance vision for atropine users. Likelihood–ratio test and Brant test was used as model diagnostics to test regression assumptions. Stata/IC15.1 (StataCorp LP, TX, USA) software was used for statistical analyses.

Results

There were no statistical significances for age and gender between the MIT and non-MIT group as shown in Table 4-1.

Table 4-1 Demographic characteristics

	MIT (n= 125)	Non-MIT (n= 122)	p-value
Age* (years)	9.72±1.54 (6.88 to 12.70)	9.56±1.29 (6.95 to 12.02)	P=0.82
Gender (male %)	52.80%	49.18%	P=0.57

* mean±sd (min to max)

The reliability tests presented as Cronbach's Alpha coefficients were listed in Table 4-2, in which all alpha values were higher than 0.70 except those in Part I General health. The Taiwan Visual Function Questionnaire (Twn VFQ-25) was considered valid for evaluating the vision related quality of life for schoolchildren in primary schools.

Table 4-2 Cronbach's Alpha of Twn VFQ-25

Cronbach's Alpha	MIT (n= 125)	Non-MIT (n= 122)
Part I General health	0.2516	0.3021
Part II Difficulty with activities	0.8747	0.8840
Part III Response to vision problems	0.7125	0.7087
Total Twn VFQ-25	0.8580	0.8708

Twn: Taiwan

The score of near activities was higher in non-MIT group (92.01 vs. 91.13), however the score of distance activities was higher in MIT group (93.00 vs. 92.89) as shown in Table 4-3. Both were not significantly different. (p=0.51 for each subscale).

Table 4-3 Comparisons between score of subscales

Score of Subscales	MIT*	n	non-MIT*	n	p-value
General Health	59.64(±27.74)	125	60.91(±27.56)	122	0.36
General Vision	66.24(±18.74)	125	66.23(±18.91)	122	0.50
Ocular Pain	89.30(±15.85)	125	88.83(±16.05)	122	0.59
Near Activities	91.13(±14.07)	125	92.01(±12.60)	122	0.51
Distance Activities	93.00(±10.25)	125	92.98(±9.79)	122	0.51
Vision Specific:					
Social Functioning	97.50(±6.74)	125	96.72(±7.67)	122	0.80
Mental Health	69.95(±10.34)	125	69.90(±9.81)	122	0.52
Role Difficulties	92.20(±13.15)	125	91.60(±13.39)	122	0.63
Dependency	74.47(±9.09)	125	74.80(±8.61)	122	0.39
Riding¶	90.90(±16.88)	92	91.18(±16.82)	94	0.45
Color Vision	95.80(±12.99)	125	95.08(±13.88)	122	0.66
Peripheral Vision	95.00(±12.70)	125	93.24(±13.65)	122	0.85

* mean±sd (min to max) ¶those who did not ride bicycle were excluded for counting "Riding".

The scores of “853240” interventions in MIT group revealed in Table 4-4a indicated that the preference rankings were 75.04(8) > 56.96(4) > 54.40(2) > 42.88 (5) > 38.72(0) > 32.00(3) respectively. Having an 8-hour sound sleep is most preferred by schoolchildren in MIT group, followed by being away from 4 3Cs, doing 2-hour outdoor activities, eating 5 colorful vegetables & fruits, taking 10-minute rest after 30-minute eye use and keeping 3 ninety-angles while sitting was the last choice.

Table 4-4a Preference score and ranking of "853240" interventions in MIT group

Intervention	8	4	2	5	0	3
n	125	125	125	125	125	125
mean	75.04	56.96	54.40	42.88	38.72	32.00
sd	30.65479	32.33454	31.17071	32.69645	29.91860	30.48003

sd: standard deviation, 8: 8-hour sound sleep, 5: 5 colorful vegetables & fruits, 3: 3-90^{o} while sitting, 2: 2-hour outdoor activities, 4: away from 4 3Cs, 0: 10-minute rest after 30-minute eye use

The correlations among “853240” interventions were shown in Table 4-4b. We found that sleeping well for “at least 8 hours (8)” had a positive correlation with “eating 5-kind of colorful vegetables and fruits daily (5)”, but negatively with all other interventions; all correlations were statistically significant except with “ 3 ninety angles (ankle, knee and hip) while sitting (3)”. Taking “2-hour outdoor activities every day (2)” had a significant negative correlation with “ being away from 4 3Cs (4)”. Having “10–minute rest every 30-minute eye use (0)” only had a positive correlation with “ being away from 4 3Cs (4)”, but not shown statistical significance.

Table 4-4b Correlations among preference scores of "853240" interventions in MIT group

	8	5	3	2	4	0
8	1.0000					
5	0.2514*	1.0000				
	0.0047					
3	-0.1047	-0.3001*	1.0000			
	0.2454	0.0007				
2	-0.2893*	-0.1188	-0.3042*	1.0000		
	0.0011	0.1869	0.0006			
4	-0.5623*	-0.4259*	0.0300	-0.1759*	1.0000	
	0.0000	0.0000	0.7398	0.0497		
0	-0.2365*	-0.3385*	-0.3448*	-0.0795	0.0769	1.0000
	0.0079	0.0001	0.0001	0.3780	0.3937	

* p-value <0.05, 8: 8-hour sleep, 5: 5 colorful vegetables & fruits, 3: 3-90° while sitting, 2: 2-hour outdoor activities, 4: away from 4 3Cs, 0: 10-minute rest after 30-minute eye use

The associations of MIT and near work (Q5 reading textbooks) with distance vision outcome (Q61 watching blackboards) adjusting for gender and age are illustrated in Table 4-5a. For MIT group, the odds of being in a higher level of Q61 (watching blackboards) are 1.25 (95% CI (0.65 - 2.41), p = 0.506) times greater than for non-MIT group, given the other variables are held constant in the model. For a one unit increase in Q5 (reading textbook), the odds of being in a higher level of Q61 (watching blackboards) are 1.03 (95% CI (1.01 - 1.05), p = 0.001) times greater given the other variables are held constant in the model. Holding the other variables at a fixed value, a one unit increase in age would result in a 0.71 (95% CI (0.55 - 0.91), p = 0.006) times lower of the odds of being in a higher level of Q61 (watching blackboards). Holding the other variables at a fixed value, for males (gender = 1), the odds of being in a higher level of Q61 (watching blackboards) are 0.61 (95% CI (0.31 - 1.20), p = 0.154) times lower than for females.

Table 4-5a The association of MIT and near work (readings) with distance vision

Ordered logistic regression — Number of obs = 247; LR chi2(4) = 23.42; Prob > chi2 = 0.0001; Log likelihood = -144.79437; Pseudo R2 = 0.0748

Q61 (watching blackboards)	Odds Ratio	[95% Conf.	Interval]	p-value
Q5 (reading textbooks)	1.03	1.01	1.05	*0.001
mit	1.25	0.65	2.41	0.506
age	0.71	0.55	0.91	*0.006
gender	0.61	0.31	1.20	0.154
/cut1	-3.38	-6.16	-0.59	
/cut2	-2.33	-5.10	0.44	

*: p-value < 0.05 level; mit: MIT = 1, non-MIT = 0; gender: male = 1, female = 0

Approximate likelihood-ratio test of proportionality of odds across response categories:
chi2(4) = 5.97
Prob > chi2 = 0.2018

Both the likelihood-ratio test (Table 5-1) and Brant test (Table 5-2) indicated that we had not violated the proportional odds assumption in this regression model. Because Q61 score would not be negative and age would not be zero, cutpoints (_cut1 and _cut2) did not reveal any clinical significance.

Table 4-5b Brant Test of Parallel Regression Assumption

Variable	chi2	p>chi2	df
All	5.52	0.238	4
Q5	3.01	0.083	1
mit	0.03	0.859	1
gender	0.08	0.777	1
age	1.16	0.282	1

Discussion

High myopia with pathologic changes, including cataract, glaucoma, retinal degeneration, macular hemorrhage and retinal detachment, is one of the leading causes of blindness (Bourke et al., 2019; Holden, Brien, 2017; Saw et al., 2005), thus delaying myopia progression is not to be overemphasized in this modern world. Atropine eye drops (Lu, P. C. & Chen, 2010; Yam et al., 2019) and orthokeratology (Chen et al., 2019; Sun et al., 2015; Tan et al., 2019) are the two most effective methods for schoolchildren to prohibit their myopia worsening to an extreme extent. In Taiwan, atropine eye drops are chosen as the main modality to treat myopia for schoolchildren due to fewer side effects and economical affordability. The consequences of pupil dilatation after installation of atropine eye drops remain the main issues of reading textbooks or newspapers, iPad, computer or smartphone as well as watching blackboards or outdoor activities for schoolchildren. The Taiwan Visual Function Questionnaire (Twn VFQ-25) was used as an instrument to measure the quality of life for the schoolchildren in primary schools.

Cronbach's Alpha coefficients of the reliability tests as listed in Table 4-2 indicated that Twn VFQ-25 was valid for evaluating the vision-related quality of life for the first grade to the sixth grade schoolchildren including MIT and Non-MIT groups.

Clinically atropine eyedrops used to control myopia progression expresses a dose-dependent patter, that is the more concentrated the better effect; however, accommodation will be deprived after pupil dilated and iris paralyzed; photophobia and difficulty in reading developed accordingly. That was annoyed. Thus we adopted three different atropine concentrations as 0.125%, 0.25% and 0.5% at different seasons to minimize the sequelae and inconvenience. (Lu, P. C. & Chen, 2010) To clarify the causes for side effects of atropine, we compared the scores between near activities and distance activities. The results in Table 4-3 revealed that the score of MIT and non-MIT group in near activities (91.13 vs. 92.01, p-value = 0.51) and distance activities (93.00 vs. 91.13, p-value = 0.51) were not significantly different. The findings suggest that accommodation deprivation caused by atropine will affect reading to a minor extent; however the reduced pseudo-myopia amount by atropine will facilitate the distance vision for those who did not wear glasses for watching blackboards or doing outdoor activities.

Textbooks reading and blackboards watching are the two most important issues for schoolchildren in their day-to-day activities. From the associations results revealed in Table 4-5a, the odds of being in a higher level of Q61 (watching blackboards) are 1.25 (95% CI (0.65 - 2.41), p = 0.506) times greater for MIT group than for non-MIT group, holding the other variables at a fixed value. For a one unit increase in Q5 (reading textbook), the odds of being in a higher level of Q61 (watching blackboards) are 1.03 (95% CI (1.01 - 1.05), p = 0.001) times greater given the other variables are held constant in the model. The results implicated that MIT program with minimal near vision affected would have a positive benefit on watching blackboards and distance vision.

While age headed an opposite direction, a one year increase in age would result in a 0.71 (95% CI (0.55 - 0.91), p = 0.006) times lower of the odds of being in a higher level of Q61 (watching blackboards), given all of the other variables in the model were held constant. Myopia getting worse while growing up with age increase, might explain this phenomenon. Females seemed to have an advantage than males from the result showing that the odds for males (gender = 1) being in a higher Q61 score level was 0.61 (95% CI (0.31 - 1.20), p = 0.154) times lower than for females (gender = 0), holding the other variables at a fixed value, even not statistically significant. Both the likelihood-ratio test (Table 4-5a) and Brant test (Table 4-5b) supported the regression model we applied.

To facilitate the benefits from foods (Donnelly et al., 2016; Ormsbee et al., 2016; Vutipongsatorn, Yokoi, & Ohno-Matsui, 2019), nature sunlight (Cao, K. et al., 2019; Guan et al., 2019; Ho, Wu, & Liou, 2019; Rose, Morgan, Ip et al., 2008), good habits for learning and daily lifestyle (Enthoven et al., 2019; Hsu et al., 2016; Lee, C. W. et al., 2017; Williams et al., 2019), we implemented the "853240" interventions in MIT group. The score results in Table 4-4a indicated that the schoolchildren in MIT group most preferred having an 8-hour sound sleep (score 75.04) followed by being away from 4 3Cs (score 56.96), doing 2-hour outdoor activities (score 54.40), eating 5 colorful vegetables & fruits (score 42.88), taking 10-minute rest after 30-minute eye use (score 38.72) and then keeping 3 ninety-angles (score 32.00) while sitting on chairs.

The correlations among "853240" interventions as shown in Table 4-4b disclosed that sleeping well for "at least 8 hours (8)" had a positive correlation with "eating 5-kind of colorful vegetables and fruits daily (5)", but negatively with all other interventions; all correlations were statistically significant except with " 3 ninety angles (ankle, knee and hip) while sitting (3)". Those findings might implicate that healthy diets improve sleep quality (Bhurosy & Thiagarajah, 2020; Cao, M., Zhu, Sun, Luo, & Jing, 2019; Cordova, Barja, & Brockmann, 2018; Min et al., 2018). The significant negative correlation between taking "2-hour outdoor activities every day (2)" and " being away from 4 3Cs (4)" implied that you would have less time for your 3Cs when you spent more time for outdoor activities because you have only 24 hours a day. Same situation applied on "having 10–minute rest every 30-minute eye use (0)” had a positive correlation with “ being away from 4 3Cs (4)”, even not shown statistical significance (p = 0.0769).

Based on the promising results above, we suggest the progressive glasses with transition and blue light filtering effects for those schoolchildren who were affected but still want to control their myopia progression with atropine. We encourage all schoolchildren to wear anti-UV sunglasses or transition glasses for outdoor activities; besides reducing use of 3-C products is the main goal, blue-light filtering glasses are also recommended while using these modern tools. Keeping healthy eating habits with more fruits and vegetables and having adequate sleep are not mandatory but beneficial for schoolchildren.

Limitations and Strengths

The strength of this study is that these data, composing primary schoolchildren from the first grade to sixth grade, were from a metropolitan citywide database that produced data prospectively. The scale of this database was big to recruit all local primary school students from all districts except some Taipei international schools, such as Taipei American School and Taipei European School. Those who were not recruited in MIT program served as control group. However, MIT program is a new intervention and focus on the modification of school-aged children daily life (Hsu et al., 2016). With the promising results with healthy interventions and minor inconveniences and side effects, we can put more efforts on the public awareness of myopia preventing.

Several limitations remain in this study. The biggest limitation is that MIT was not randomized because most parents and the government desired the schoolchildren's myopia will be well controlled, and thus MIT vs. non-MIT could be different in many ways. We cannot exclude the presence of undetected bias because the responses form interviewing with young children. Selection biases might arise from the fact that most subjects used for analyses were from highly educated parents who worked in high-tech industrial or top-ranked financial companies located at the Neihu Science Park, comparable to Silicon Valley in California. We attempt to minimize selection bias by adjusting all obtainable demographics and comorbidities, but still some potential confounders such as compliance to MIT program or combining with alternative regimens (Chinese herbs, acupuncture) were not addressed. Atropine concentrations are not recorded clearly within database. There were differences of lifestyle and education pressure between urban and rural schools as well as local and international school. Putting the regular daily activities including reading textbooks and watching blackboards in Taiwan Visual Function Questionnaire (Twn VFQ) to fit children's day-to-day life might affect the score of some subdomains. The results give some inputs and practical concerns to public health. A big-scale longitudinal study in the future is needed for generalization of the results to other populations.

Chapter 5

Discussion

Myopia is getting global public concern in the twenty-first century owing to the recent rise in its prevalence worldwide and associated ocular disease burden (Harb & Wildsoet, 2019); the situation is most serious in East Asia (Harb & Wildsoet, 2019; Mak, Yam, Chen, Lee, & Young, 2018; Prousali et al., 2019). In Taiwan, myopia prevalence of primary schoolchildren is the second highest worldwide which progressed at the rate around 1.0 - 1.2D per year, if by glasses wearing only without any other treatment (Chang, 1999; HPA, 2018; Liou, 2019). Myopia starting at early age is easy to become high myopia later on (Chua et al., 2016) and brings a tremendous public health and socio-economic burden (Bourke et al., 2019).

The traditional high concentration (1.0%) atropine eye drops was most effective but caused difficulties with near work and severe photophobia for outdoor activities (Han, W. T. et al., 2019; Tran et al., 2018). OK lenses, even costly and having corneal side effects, are used alone (Cho & Cheung, 2012) or combined with atropine (Chen et al., 2019; Sun et al., 2015; Tan et al., 2019) to prevent myopia progression. The new trial of low concentration (0.01%, 0.025%, 0.05%) atropine revealed some kind of dose-dependent efficacy (Tran et al., 2018; Yam et al., 2019) the data were suspicious of lack of evidence-based support (Brennan & Cheng, 2019). The multifocal spectacles existed the waning effect to reduce myopia progression over long-term follow-up (Brennan & Cheng, 2019; Holden, B. et al., 2014; Kaphle et al., 2019). Among all the methods mentioned above trying to prevent or slow down the progression of myopia, atropine eye drops are the most economic and reliable treatments. Taiwan is located at subtropical area passed by the Tropic of Cancer; the weather is hot in summers with intensive sunlight, warm in springs and cool in autumns with moderate sunlight, and a little cod in winters with mild sunshine. To avoid the side effects of photophobia and difficulties with near works, we use medium-concentration atropine (0.125%, 0.25%, 0.5%) eye drops based on sunlight intensity in various seasons to delay myopia progression for primary schoolchildren.

The pros and cons of different treatment modalities are summarized and illustrated n Table 5-1.

Table 5-1 Pros & cons of different modality for myopia control

Modality	Pros	Cons
1.0% Atropine	most effective	difficulties with near work, severe photophobia for outdoor activities (Han, Rong, & Xu, 2019; Tran et al., 2018)
OK lens	effective	expensive, corneal side effects used alone (Cho & Cheung, 2012) or combined with atropine (Chen et al., 2019; Sun et al., 2015; Tan, Ng, Cheng, Woo, & Cho, 2019)
low concentration (0.01%, 0.025%, 0.05%)	dose-dependent efficacy (Tran et al., 2018; Yam et al., 2019)	lack of evidence-based support (Brennan & Cheng, 2019)
multifocal spectacles	controversial	waning effect to reduce myopia progression over long-term follow-up (Brennan & Cheng, 2019; Holden et al., 2014; Kaphle, Atchison, & Schmid, 2019).
modified medium concentration (0.125%, 0.25%, 0.5%)	cost-effective, friendly, economic and reliable	some difficulties with near work or photophobia for outdoor activities under strong sunlight

The evidences of familial aggregation, and genetic factors suggest the pathogenesis of myopia, especially high myopia (Cai et al., 2019; Mutti et al., 2002); several candidate myopia genes have been identified by gene-based analyses (Flitcroft et al., 2018). Environmental influences and gene-environment interactions get more attention to explain the myopiagenesis (Harb & Wildsoet, 2019; Miraldi Utz, 2017;

Morgan & Rose, 2019; Tedja et al., 2019; Vishweswaraiah et al., 2019) Urbanization, educational pressure with intensive reading and near works, too long indoor activities and insufficient outdoor time with sunlight exposure (Cao, K. et al., 2019; Guggenheim et al., 2012; Morgan & Rose, 2019; Shapira et al., 2019), poor eating habitats with nutrients imbalance are the common environmental risk factors. Heredity is the factor beyond our ability to change; hence medical and environmental interventions remain the main strategies to prevent myopia progression in this century. We emphasize on healthy life styles with "853240" daily implementation in additional to atropine eye drops treatment.

During 5-year follow-up, mean myopia progression is 1.69 ±1.06 D and 3.24±1.08 D in MIT and non-MIT group (P=0.0000), respectively (Table 2-1b, Chapter 2); and mean myopia progression per year was 0.33±0.0004 D/y and 0.64 ±0.0006 D/y in MIT and non-MIT group (P=0.000), respectively (Table 2-5a, Figure 2-4a, Chapter 2).

The axial elongation between MIT and non-MIT group differed significantly from year 0.5 till year 5 follow-ups. The axial elongations were 0.075±0.09 mm and 0.10±0.108 mm in MIT and non-MIT group (P=0.0015) at year 0.5; 0.67±0.30 mm and 1.01±0.44 mm in MIT and non-MIT group (P=0.0000) at year 5 respectively (Table 2-3b, Chapter 2). Myopia progressed as 1.44 ±0.04D /mm in non-MIT group more than 1.06 ±0.05D /mm in MIT group (Fig 2-3b, Chapter 2). The results above combined with Singapore finding in a Magnetic Resonance Imaging (MRI) study of 3-D eye shape indicate that the longer the eye, the worse the myopia; where axial lengths elongation remain as a biomarker for myopia progression (Matsumura et al., 2019).

The results in Chapter 2 suggest that seasonally modified medium-concentration (0.125%, 0.25% and 0.5%) atropine eye drops integrated with healthy lifestyle “853240” interventions at school and home should take an important position for preventing myopia from progression among primary schoolchildren.

In addition to more prominent in delaying myopia progression for MIT group, the economic issues are important to those parents as well. In Chapter 3, we further perform the cost-effectiveness analysis between MIT (n = 364) and non-MIT (n = 174) group from year 0.5 to year 5.0 follow-ups. Most parents will consider not only the effects of myopia control, but also the economic burden following treatments for their primary schoolchildren. Compared to orthokeratology (OK) lenses, atropine eye drops win the popularity for preventing myopia progression in Taiwan because of its easiness for use and minimal out-of-pocket expenditure or co-payment. The cost of a total 113 Singaporean aged 40 years and older with myopia at least -0.5 diopters is not only a considerable economic load up to USD 755 million per year but also a huge public health impact. (Zheng et al., 2013) MIT program gives the parents motives for seeking effective treatment to delay myopia progression by providing financial supports and reliable ophthalmic examinations in Taipei City.

Considering cost, out-of-pocket expenditure is a minor issue because of some schoolchildren coming from areas within walking distance to clinic, the convenience of public transportation (bus, MRT, U-bike) in Taipei City and some free parking spaces provided by clinic for parents or private drivers. The mean costs shown in Figure 3-2 of Chapter 3 are higher in MIT than non-MIT group, climbing up from year 0.5 (ΔNTD 158.16 = ΔUSD 5.26), year 1.0 (ΔNTD 317.41 = ΔUSD 10.57), year 2.0 (ΔNTD 644.63 = ΔUSD 21.46), and to the top at year 3.0 with the most disparity (ΔNTD 981.97 = ΔUSD 32.69), then sliding down to year 4.0 (ΔNTD 692.46 = ΔUSD 23.05) and to the second lowest at year 5.0 (ΔNTD 393.999 = ΔUSD 13.11). Those are the trends of incremental costs between MIT and non-MIT group.

The mean effect gaps (Δdse) between MIT and non-MIT shown in Figure 3-1, Chapter 3 getting larger indicates the effects of myopia control are more evident at year 5.0 (Δdse = 3.24-1.69 = 1.55D) than year 0.5 (Δdse = 0.26-0.17 = 0.09D). The more myopia progression the worse outcome, thus myopia has detrimental effect and MIT group revealed a better outcome than non-MIT group (1.69D vs. 3.24D) at year 5.0. The mean costs shown in Table 3-3b, Chapter 3 are 930.14 and 771.98 for MIT and non-MIT group respectively.

As shown in Figure 3-5, Chapter 3, Incremental Cost-Effectiveness Ratios (ICERs) keep sliding pattern whatever willing-to-pay varies from 10 to 300 or even to 1,000; however, after the turning-point at year 3.0, Incremental Net Benefit (INB) for w2p (1000) presents a value of 439.099 at year 4.0 and climbs up to value of 1159.578 at year 5.0. The result of low ICER and high INB indicates that the modified atropine use in MIT group, compared to non-MIT group, reveals cost-effective after following-ups for ≥ 4 years as long as willing-to-pay equal to or higher than NTD 1,000. The results of ICERs, between MIT and non-MIT group, dropping from 1837.305 at year 0.5 dramatically to 253.602 at year 5.0 are implicated that for delaying myopia progression, the costs will decrease more and more for long-term atropine eye drops use modified with seasonal change and the severity of myopia. And INB under w2p (1000) turning from -72.078 at year 0.5 to 1159.578 at year 5.0 suggest a desirable investment for the government, not only to prevent ocular deterioration from high myopia but also to reduce cost of healthcare. Further researches should aim to develop and provide more solid and longitudinal data to generalize the economic model.

There is no previous cost-effectiveness study ever been conducted on the combination therapy of modified atropine eye drops in a High-tech Science Park with high income setting to allow comparison of results.

We wonder the impacts of pupil dilatation on school children's daily activities and learning. Regarding atropine eye drops, is there any serious side effect after long-term use? Is there any difference for half-year use and 5-year use? To reply those parents' deep concerns, in Chapter 4 we analyze the consequences of pupil dilatation after installation of atropine eye drops, especially in near vision (reading textbooks or newspapers, iPad, computer or smartphone) and distance vision (watching blackboards or outdoor activities) for schoolchildren. The Taiwan Visual Function Questionnaire (Twn VFQ-25) (Hinterlong et al., 2019; RAND, 2019)is used to measure the quality of life for the schoolchildren in primary schools.

Because the recruited MIT subjects in the previous two studies are all of 2nd grade and same-aged primary schoolchildren, after five-year treatment with atropine eye drops, should adapted atropine well. In this study, we recruit a total of 247 primary schoolchildren from first grade to sixth grade as long as they have used atropine for at least sixe months. There are 125 and 122 subjects recruited for MIT and non-MIT group respectively to test the validity of Twn VFQ-25 questionnaire and analyze the impacts of atropine eye drops on children's day-to-day activities.

Cronbach's Alpha coefficients listed in Table 4-2, Chapter 4 indicate that Twn VFQ-25 is valid for evaluating the vision-related quality of life for the first grade to the sixth grade schoolchildren for both MIT and Non-MIT groups.

Atropine eye drops reveal dose-dependence for treatment effect and side effect as well. The annoying effect of pupil dilatation caused by atropine is minimized by using three medium-concentrations as 0.125%, 0.25% and 0.5% seasonally (Lu, P. C. & Chen, 2010). The results in Table 4-3, Chapter 4 revealed that the score of MIT and non-MIT group in near activities (91.13 vs. 92.01, p-value = 0.51) and distance activities (93.00 vs. 91.13, p-value = 0.51) were not significantly different. The result implies that accommodation deprived by atropine will affect reading in a minor extent; however the reduced pseudo-myopia amount by atropine will facilitate the distance vision for those who did not wear glasses for watching blackboards or doing outdoor activities.

Textbooks reading and blackboards watching are the two most important issues for schoolchildren in their daily life. From the associations results revealed in Table 4-5a, Chapter 4, the odds of being in a higher level of Q61 (watching blackboards) are 1.25 (95% CI (0.65 - 2.41), p = 0.506) times greater for MIT group than for non-MIT group, holding the other variables at a fixed value. For a one unit increase in Q5 (reading textbook), the odds of being in a higher level of Q61 (watching blackboards) are 1.03 (95% CI (1.01 - 1.05), p = 0.001) times greater given the other variables are held constant in the model. The results are implicated that MIT program with minimal near vision affected would have a positive benefit on watching blackboards and distance vision.

While age headed an opposite direction, a one year increase in age would result in a 0.71 (95% CI (0.55 - 0.91), $p = 0.006$) times lower of the odds of being in a higher level of Q61 (watching blackboards), given all of the other variables in the model were held constant. This result might explain the phenomenon that myopia getting worse while growing older. Females seemed to have an advantage than males from the result showing that the odds for males (gender = 1) being in a higher Q61 score level was 0.61 (95% CI (0.31 - 1.20), $p = 0.154$) times lower than for females (gender = 0), holding the other variables at a fixed value, even not statistically significant. Both the likelihood-ratio test (Table 4-5a, Chapter 4) and Brant test (Table 4-5b, Chapter 4) supported the applied regression model.

To facilitate the benefits from foods (Donnelly et al., 2016; Ormsbee et al., 2016; Vutipongsatorn et al., 2019), nature sunlight (Cao, K. et al., 2019; Guan et al., 2019; Ho et al., 2019; Rose et al., 2008), good habits for learning and daily lifestyle (Enthoven et al., 2019; Hsu et al., 2016; Lee, C. W. et al., 2017; Williams et al., 2019), we implemented the “853240” interventions in MIT group. The score ranking results in Table 4-4a, Chapter 4 suggest that the schoolchildren in MIT group most preferred having an 8-hour sleep (score 75.04) followed by being away from 4 3Cs (score

56.96), doing 2-hour outdoor activities (score 54.40), eating 5 colorful vegetables & fruits (score 42.88), taking 10-minute rest after 30-minute eye use (score 38.72) and then keeping 3 ninety-angles (score 32.00) while sitting on chair.

The correlations among “853240” interventions as shown in Table 4-4b, Chapter 4 disclosed that sleeping well for “at least 8 hours (8)” had a positive correlation with “eating 5-kind of colorful vegetables and fruits daily (5)”, but negatively with all other interventions; all correlations were statistically significant except with “ 3 ninety angles (ankle, knee and hip) while sitting (3)”. Those results agree with other studies for healthy diets to improve sleep quality (Bhurosy & Thiagarajah, 2020; Cao, M. et al., 2019; Cordova et al., 2018; Min et al., 2018). The significant negative correlation between taking “2-hour outdoor activities every day (2)” and “ being away from 4 3Cs (4)” implies that you should have less time for your ICs when you spend more time for outdoor activities because you have 24 hours a day only. “Having 10–minute rest every 30-minute eye use (0)” reveals no significantly (p = 0.0769) positive correlation with “ being away from 4 3Cs (4)”.

Based on the promising results above, we suggest the progressive glasses with transition and blue light filtering effects for those schoolchildren who were affected but still want to control their myopia progression with atropine. We encourage all schoolchildren to wear anti-UV sunglasses or transition glasses for outdoor activities. Reducing use of 3-C products is the main goal as a healthy habit, blue-light filtering glasses are also recommended while using these modern tools. Keeping healthy eating habits with more fruits and vegetables and having adequate sleep are not mandatory but beneficial for schoolchildren.

Study Limitations

Several limitations remain in this study. First, the biggest limitation is that MIT was not randomized and confined with small sample size. Second, we cannot exclude the presence of undetected bias because the responses form interviewing with young children. Selection biases might arise from the fact that most subjects used for analyses were from highly educated parents who worked in high-tech industrial or top-ranked financial companies. We attempt to minimize selection bias by adjusting all obtainable demographics and comorbidities, but still some potential confounders such as compliance to MIT program or combining with alternative regimens (Chinese herbs, acupuncture, ear magnet etc.) were not addressed. Third, relative costs and effectiveness of atropine therapy may vary between populations. Fourth, there were differences of lifestyle and education pressure between urban and rural schools as well as local and international schools. Putting the regular daily activities including reading textbooks and watching blackboards in Taiwan Visual Function Questionnaire (Twn VFQ-25) to fit children's day-to-day life might affect the score of some subdomains. Fifth, the scheduled frequency for eye exam as twice a year only is not enough to keep effective treatment for those who did not spend more time to visit the ophthalmic clinic.

Study strength

The strength of this study is that our data were from a metropolitan citywide database that produces data prospectively. The scale of this database was big to recruit all local public primary school students from all districts except several private or international schools, such as Taipei American School, Taipei European School or Taipei Japanese School. Those who were not recruited in MIT program served as controls. A 5-year longitudinal follow-up provided a chance to evaluate the long-term effect of myopia control. MIT program is a new intervention and focus on the modification of schoolchildren day-to-day life (Hsu et al., 2016). This prospective and longitudinal study confirms that combination of 0.125%, 0.25% and 0.5% atropine as well as daily life interventions “853240” of MIT group are more effective than irregular therapy regimen. All schoolchildren completed the 5-year follow-up without major side effects reported.

Economic evaluations can provide “value-for-money” information to those decision-makers about the allocation of limited health care resources and can be used to identify the worthy interventions for treatments and therapies. (Mitton et al., 2014) The cost-effectiveness analysis has implicated that for delaying myopia progression; the costs will decrease more and more for long-term atropine eye drops use modified with seasonal change and the severity of myopia.

Conclusions

There are three important tips for this study:

1. "Atropine+853240" playing positive role in delaying myopia progression.
2. "Atropine+853240" becoming low ICER & high INB if persisting $\geq$ 4-5y.
3. "Atropine+853240" not causing major inconvenience for quality of life.

Public Health Implications

We thus propose that MIT program should be expanded to other urban and rural schools and extended to kindergarten, junior high schools and even to high schools for more effective control of myopia progression. This is a worthy investment for the government, not only to prevent ocular deterioration to high myopia but also reduce the cost of healthcare. Besides, this health issue deserves public prevention concern and a further longitudinal investigation in big dataset for generalization. Like the fighting strategy for COVID-19 pandemic: treat earlier, recover faster with less complications; myopia treatment should start as early as possible.

References

Appendix

PB/IA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(INTERVIEWER ADMINISTERED FORMAT)

January 2000

RAND hereby grants permission to use the "National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25) July 1996, in accordance with the following conditions which shall be assumed by all to have been agreed to as a consequence of accepting and using this document:

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Instructions:

I'm going to read you some statements about problems which involve your vision or feelings that you have about your vision condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing them.

指導語

我要讀一些句子，包括：你視力造成的問題，或你對你視力情況的感覺。在我讀完句子後，請你選出跟你的情況最相近的答案。

如果你有戴眼鏡或隱形眼鏡，請用戴上眼鏡或隱形眼鏡的情況，回答所有的問題！

請依照你需要的時間回答每一個問題。你所有的答案都是保密的。這個調查是為了增加我們對視力有關的知識，以及怎麼樣改善你的生活品質。請儘可能正確的回答，請記得：如果你活動的時候有戴眼鏡或隱形眼鏡，就用戴上眼鏡或隱形眼鏡的情況回答。

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Visual Functioning Questionnaire - 25
視力功能問卷 - 25

PART 1 - GENERAL HEALTH AND VISION
第一部分 - 健康和視力

1. In general, would you say your overall health is*:
一般而言, 你覺得自己整體的健康狀況如何

(Circle One)

READ CATEGORIES:

Excellent 非常好	1
Very Good 很好	2
Good 好	3
Fair 普通	4
Poor 不好	5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?
目前你覺得你的雙眼視力(若你是配戴眼鏡或隱形眼鏡,請用矯正後視力回答)如何?

(Circle One)

READ CATEGORIES:

Excellent 非常好	1
Good 好	2
Fair 普通	3
Poor 差	4
Very Poor 很差	5
Completely Blind 全盲	6

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* Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0

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3. How much of the time do you worry about your eyesight?
你會花多少時間擔心你的視力?

(Circle One)

READ CATEGORIES:

None of the time 從不 1
A little of the time 偶爾 2
Some of the time 有時 3
Most of the time 經常....................... 4
All of the time 總是........................... 5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:
你眼睛是否會感到疼痛或不舒服(例如:灼熱感,癢,刺痛),達到以下何程度

(Circle One)

READ CATEGORIES:

None 無...1
Mild 輕微... 2
Moderate 中度.................................. 3
Severe, or 不適.................................. 4
Very severe? 極度不適.................... 5

PART 2 - DIFFICULTY WITH ACTIVITIES
第二部分 – 影響活動

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.
接下來是關於你戴眼鏡或隱形眼鏡從事較精細的活動時, 是否因此感到困擾?

5. How much difficulty do you have reading ordinary print in newspapers (textbooks)? Would you say you have:
你在閱讀報章雜誌 (課本或課外讀物) 時, 是否感到吃力?
(READ CATEGORIES AS NEEDED) *(Circle One)*

No difficulty at all 沒有困擾..…………………... 1
A little difficulty 些微.. 2
Moderate difficulty 還好... 3
Extreme difficulty 非常困擾.. 4
Stopped doing this because of your eyesight 因視力造成無法閱讀… 5
Stopped doing this for other reasons or not interested in doing this 因其他因素而不閱讀............................. 6

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6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:

你是否在從事近距離工作時(例如:畫圖或玩樂高 烹飪,縫紉,修繕),會感到困擾?

(READ CATEGORIES AS NEEDED) *(Circle One)*

No difficulty at all 沒有困擾	1
A little difficulty 些微	2
Moderate difficulty 還好	3
Extreme difficulty 非常困擾	4
Stopped doing this because of your eyesight 因視力造成無法閱讀	5
Stopped doing this for other reasons or not interested in doing this 因其他因素而不閱讀	6

6.1 How much difficulty do you have watching blackboards ? Would you say:

你是否在看黑板時,會感到困擾?

(READ CATEGORIES AS NEEDED) *(Circle One)*

No difficulty at all 沒有困擾	1
A little difficulty 些微	2
Moderate difficulty 還好	3
Extreme difficulty 非常困擾	4
Stopped doing this because of your eyesight 因視力造成無法閱讀	5
Stopped doing this for other reasons or not interested in doing this 因其他因素而不閱讀	6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

依照你目前的視力狀況, 你是否在塞滿東西的架子上尋找物品時, 會感到困擾?

(READ CATEGORIES AS NEEDED) *(Circle One)*

No difficulty at all 沒有困擾	1
A little difficulty 些微	2
Moderate difficulty 還好	3
Extreme difficulty 非常困擾	4
Stopped doing this because of your eyesight 因視力造成無法繼續	5
Stopped doing this for other reasons or not interested in doing this 因其他因素而不繼續	6

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8. How much difficulty do you have reading street signs or the names of stores?
你是否在看路標或招牌時,感到困擾?

(READ CATEGORIES AS NEEDED) *(Circle One)*

No difficulty at all 沒有困擾	1
A little difficulty 些微	2
Moderate difficulty 還好	3
Extreme difficulty 非常困擾	4
Stopped doing this because of your eyesight 因視力造成無法繼續	5
Stopped doing this for other reasons or not interested in doing this 因其他因素而不繼續	6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?
依照你目前的視力狀況, 你是否在昏暗光線下或夜晚下樓梯、走小路時而感到困擾?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 沒有困擾	1
A little difficulty 些微	2
Moderate difficulty 還好	3
Extreme difficulty 非常困擾	4
Stopped doing this because of your eyesight 因視力造成無法繼續	5
Stopped doing this for other reasons or not interested in doing this 因其他因素而不繼續	6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?
依照你目前的視力狀況, 當你走在路上時, 要注意週邊的事物,是否感到困擾?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 沒有困擾	1
A little difficulty 些微	2
Moderate difficulty 還好	3
Extreme difficulty 非常困擾	4
Stopped doing this because of your eyesight 因視力造成無法繼續	5
Stopped doing this for other reasons or not interested in doing this 因其他因素而不繼續	6

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11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

依照你目前的視力狀況, 當你在交談時, 對於觀察對方的反應, 是否感到困擾?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 沒有困擾.. 1
A little difficulty 些微.. 2
Moderate difficulty 還好.. 3
Extreme difficulty 非常困擾.. 4
Stopped doing this because of your eyesight 因視力造成無法繼續........ 5
Stopped doing this for other reasons or not interested in doing this 因其他因素而不繼續.. 6

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

依照你目前的視力狀況, 對於挑選和搭配服裝, 是否感到困擾?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 沒有困擾.. 1
A little difficulty 些微.. 2
Moderate difficulty 還好.. 3
Extreme difficulty 非常困擾.. 4
Stopped doing this because of your eyesight 因視力造成無法繼續........ 5
Stopped doing this for other reasons or not interested in doing this 因其他因素而不繼續.. 6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants ?

依照你目前的視力狀況, 是否在出席社交場合(家庭聚會,派對,聚餐)時感到困擾?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 沒有困擾.. 1
A little difficulty 些微.. 2
Moderate difficulty 還好.. 3
Extreme difficulty 非常困擾.. 4
Stopped doing this because of your eyesight 因視力造成無法繼續........ 5
Stopped doing this for other reasons or not interested in doing this 因其他因素而不繼續.. 6

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14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events under sunlight?
依照你目前的視力狀況, 對於外出看電影, 在陽光下遊玩或運動時是否會產生困擾?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 沒有困擾	1
A little difficulty 些微	2
Moderate difficulty 還好	3
Extreme difficulty 非常困擾	4
Stopped doing this because of your eyesight 因視力造成無法繼續	5
Stopped doing this for other reasons or not interested in doing this 因其他因素而不繼續	6

15. Now, I'd like to ask about drving a car (riding a bike). Are you currently driving (bicycling), at least once in a while?

你目前有在開車（騎腳踏車, 溜冰, 溜直排輪, 滑板車）嗎?

(Circle One)

Yes 是	1	*Skip To Q 15c*
No 否	2	

15a. IF NO, ASK: Have you never driven a car (ridden a bike) or have you given up driving (riding)?
如果沒有:你是不曾開車(騎腳踏車)還是已經沒有在開車(騎腳踏車)?

(Circle One)

Never drove 從不	1	*Skip To Part 3, Q 17*
Gave up 放棄	2	

15b. IF GAVE UP DRIVING(RIDING): Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?
如果你是後來放棄開車（騎腳踏車）: 是什麼原因讓您放棄的?

(Circle One)

Mainly eyesight 視力的問題	1	*Skip To Part 3, Q 17*
Mainly other reasons 其他原因	2	*Skip To Part 3, Q 17*
Both eyesight and other reasons 以上皆是	3	*Skip To Part 3, Q 17*

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15c. IF CURRENTLY DRIVING: How much difficulty do you have driving (riding) during the daytime in familiar places? Would you say you have:
如果你目前有在開車(騎腳踏車): 白天在熟悉的路段駕駛時, 是否會有困擾?

(Circle One)

No difficulty at all 沒有困擾........................ 1
A little difficulty 些微.................................. 2
Moderate difficulty 還好............................... 3
Extreme difficulty 非常困擾.......................... 4

16. How much difficulty do you have driving (riding) at night? Would you say you have: (READ CATEGORIES AS NEEDED)
在夜間駕駛（騎腳踏車）時, 是否感到困擾?

(Circle One)

No difficulty at all 沒有困擾.. 1
A little difficulty 些微... 2
Moderate difficulty 還好.. 3
Extreme difficulty 非常困擾... 4
Have you stopped doing this because
of your eyesight 因視力造成無法繼續.. 5
Have you stopped doing this for otherreasons
or are you not interested in doing this 其他因素而無法繼續..... 6

16a. How much difficulty do you have driving (riding) in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:
在較困難的駕駛(騎腳踏車)情境下, 例如:天氣不好, 尖峰時段, 高速公路或在市區內駕駛, 你是否會感受到困擾?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 沒有困擾.. 1
A little difficulty 些微... 2
Moderate difficulty 還好.. 3
Extreme difficulty 非常困擾... 4
Have you stopped doing this because
of your eyesight 因視力造成無法繼續.. 5
Have you stopped doing this for otherreasons
or are you not interested in doing this 其他因素而無法繼續..... 6

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PART 3: RESPONSES TO VISION PROBLEMS

第三部分– 視力造成的問題

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

接下來的問題是關於視力是否影響到你從事的事情, 針對每一個問題, 就發生的頻率作答

(Circle One On Each Line)

READ CATEGORIES:	All of the time 總是	Most of the time 經常	Some of the time 有時	A little of the time 偶爾	None of the time 從沒
17. Do you accomplish less than you would like because of your vision? 因為你的視力, 造成你完成的事情比預期的少?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision? 因為你的視力, 是否限制了你工作的時間或從事某些活動?	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say: 是否因為眼內或眼周的痛或不適(例如:灼熱感,癢,刺痛)而讓你無法做你有興趣的事情?	1	2	3	4	5

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For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.
以下敘述，請按照題號圈出與你情況相同的數字。

(Circle One On Each Line)

	Definitely True 絕對是	Mostly True 大多數是	Not Sure 不確定	Mostly False 大多不是	Definitely False 絕對不是
20. I stay home most of the time because of my eyesight. 因為我視力的關係, 我大多數時間都待在家裡	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight. 因為我視力的關係, 我經常感到受挫	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight. 因為我視力的關係, 我經常沒有辦法控制自己的行為	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me 因為我視力的關係, 我過度依賴他人告知我事情	1	2	3	4	5
24. I need a lot of help from others because of my eyesight. 因為我視力的關係, 我需要得到更多幫助	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight. 因為我的視力, 我害怕我做的事情造成自己或他人不便	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.

訪問結束，謝謝你的時間及幫助。

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Curriculum Vitae

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- 07/01/1980 ~ 06/30/1984 Chemical Engineering, National Taiwan University, Taipei, Taiwan; B.S.
- 07/01/1987 ~ 06/30/1992, Chang Gung Medical College, Taoyuan, Taiwan; M.D.

Post-Graduate Education : (Date, Department, Graduate School, Location, Degree - M.S. or M.A. or Ph.D)

- 07/01/1998 ~ 05/31/1999, Harard School of Public Health, Boston MA, USA; M.S.
- 07/01/1997 ~ 08/31/1999, Masachusetts Eye & Ear Infirmary and Schepens Eye Research Institute, Harvard Medical School, Boston MA, USA, Research Fellow
- 09/15/2012 ~ 04/03/2020, Department of Health Policy and Management, Bloomburg School of Public Health, Johns Hopkins University, Baltimore, MD, USA, DrPH

Academic Appointment (Including Teaching Experience):

- 5/1/1998 ~ 8/31/1999 Coordinator, Fellow training program, Masachusetts Eye & Ear Infirmary and Schepens Eye Research Institute, Harvard Medical School, Boston MA, USA.
- 9/1/1999 ~ 12/20/2001, Coordinator, resident and fellow training program, Chang Gung Memorial Hospital Taipei, Taiwan

- 9/1/1999 ~ 12/20/2001, Coordinator, resident and fellow training program, Chang Gung Memorial Hospital Taipei, Taiwan
- 12/21/2001 ~ present, Chairman, resident and fellow training program, Chang Gung Memorial Hospital Chia Yi, Taiwan
- 7/1/2001 ~ 6/30/2005, Academic consultant, Dept. Education)
- 7/1/2003 ~ 6/30/2005, Assistant professor, Chang Gung University & Institute of Technology, Taiwan
- 8/1/2005 ~ 12/31/2006, Clinical Associate Professor, School of Medicine, Tzu Chi University, Hualien, Taiwan
- 9/15/2006 ~ 6/30/2008, Adjunct Professor, Oriental Institute of Technology, Taipei, Taiwan

Employment Record : (Date,Title, Department, Hospital of Institutions, Location)

- 07/01/1996 ~ 12/21/2001, Ophthalmology, Chang Gung Memorial Hospital, Taipei, Taiwan
- 12/21/2001 ~ 5/15/2005, Chairman, Ophthalmology, Chang Gung Hospital Chia Yi, Taiwan
- 05/21/2005 ~ 12/31/2006, Chairman,Ophthalmology, Buddhist Tzu Chi Hospital, Taipei, Taiwan
- 01/08/2007 ~ 12/31/2009, Superintendent, Shin Ho Mei Clinic Group, ChiaYi & Taipei, Taiwan
- 02/01/2010 ~ present, Superintendent, Harvard Vision Center, Taipei, Taiwan

Professional Affiliations: (Medical Organizations or Societies)

- 12/01/2002 ~ 11/30/2005, Coordinator, member service committee of transaction of Ophthalmological Society of the Republic of China
- 03/16/2000 ~06/31/2004, President, Chang Gung University Alumni Association
- 01/01/2001 ~12/31/2003, Supervisor, Harvard Club Republic of China
- 01/01/2003 ~ present, Director, Harvard Club Republic of China
- 01/16/2006 ~ 01/15/2010, Director, Taiwanese Society of Cataract and Refractive Surgeons

Professional Activities: (Including Administrative Experience, Committee Membership, editorial Boards of Journals, etc.)

1. American Academy of Ophthalmology (AAO, 223411)
2. Association for Research in Vision and Ophthalmology (ARVO, 49618)
3. American Society of Cataract and Refractive Surgery (ASCRS, 082368)
4. European Society of Cataract and Refractive Surgery (ESCRS, 6502)
5. Transaction of Ophthalmological Society of Taiwan (000931)
6. Laser Medicine Society of Taiwan (2215)

Research Project: (Please list in research subject, research grant from the institutions and research records no, as HMRP, NMRP, CMRP, etc. by yearly)

Paul Chung-Shien Lu	Using immunochemical fingerprint technique to identify the endogenous digoxin-like substances in normal and cataract human lens (NSC87-2314-B182A-038)	Associated researcher	1997.8~1999.7	National Science Council
Paul Chung-Shien Lu	The correlation between the formation of cataract and free radicals (CMRP542)	Associated researcher	1997.7-1998.6	Chang Gung Memorial Hospital
Paul Chung-Shien Lu	Matrix metalloproteinases expression in corneal wound (NEI 10101)	Associated Principal investigator	1999.9-2003.8	NIH USA
Paul Chung-Shien Lu	Angiostatin expression in corneal wound (CMRP1319)	Principal investigator	2002.7-2003.7	Chang Gung Memorial Hospital
Paul Chung-Shien Lu	Etiopathogenic study of pterygium by genetic technology platform (CMRPG62002)	Principal investigator	2003.8-2004.7	Chang Gung Memorial Hospital
Paul Chung-Shien Lu	Basic Vision Care Program for Elderly in ChiaYi County (DOH93-HP-1311)	Principal investigator	2004.6-2005.3	Bureau of Health Promotion, Dpt. Of Health, Taiwan
Paul Chung-Shien Lu	Deep lamellar endothelial keratoplasty (DLEK) as an alternative for corneal endothelial failure compared to traditional penetrating keratoplasty (PKP). (CMRPG63008)	Principal investigator	2004.11-2005.10	Chang Gung Memorial Hospital

Publications:

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3. Azar DT, Lu PC. Consultation section. Refractive surgical problem. J Cataract Refract Surg 1997;23:1137-1138.(SCI:2.130)
4. Maeda M, Vanlandingham BD, Ye H, Lu PC, Azar DT. Immunoconfocal localization of gelatinase B expressed by migrating intrastromal epithelial cells after deep annular excimer keratectomy. Curr Eye Res 1998;17:836-843. (SCI:1.300)
5. Lu PC, Ye H, Maeda M, Azar DT. Immunolocalization and gene expression of matrilysin during corneal wound healing. Invest Ophthalmol Vis Sci 1999;40:20-27. (SCI:5.250)
6. Colby K, Lu P, Ou R, Azar D. Comparison of LASIK and PRK for the correction of moderate myopia and myopic astigmatism. Asia-Pacific J Ophthalmol 1999;11:2-6.
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